UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY and MANULIFE INSURANCE COMPANY, Plaintiffs, v. ABBOTT LABORATORIES, Defendant.	CIVIL ACTION NO. 05-11150-DPW

ABBOTT'S CORRECTED DEPOSITION DESIGNATIONS FOR LYNN KLOTZ

Defendant Abbott Laboratories ("Abbott") respectfully submits the attached corrected deposition designations for the November 16, 2006 and May 16, 2007 depositions of Lynn Klotz, Scientific Consultant for Hancock.

.

.

Dated: February 22, 2008

Respectfully submitted,

ABBOTT LABORATORIES

By: __/s/ Eric J. Lorenzini_____
Eric J. Lorenzini

Jeffrey I. Weinberger (*pro hac vice*)
Gregory D. Phillips (*pro hac vice*)
Eric J. Lorenzini *(pro hac vice)*
Ozge Guzelsu *(pro hac vice)*
MUNGER, TOLLES & OLSON LLP
355 South Grand Avenue, Thirty-Fifth Floor
Los Angeles, CA 90071-1560
Tele: (213) 683-9100

and

Peter E. Gelhaar (BBO#188310)
Michael S. D'Orsi (BBO #566960)
DONNELLY, CONROY & GELHAAR LLP
1 Beacon St., 33rd Floor
Boston, Massachusetts 02108
(617) 720-2880
peg@dcglaw.com
msd@dcglaw.com

Counsel for Abbott Laboratories

CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 22, 2008.

Date: February 22, 2008.

/s/ Ozge Guzelsu

Lynn Klotz Deposition Designations

Depo Date	Witness	Hancock Designation	Abbott Counter Designatio	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
11/16/06	Klotz, Lynn			6:13-6:15			
11/16/06	Klotz, Lynn			6:19-7:7			
11/16/06	Klotz, Lynn			14:8-15:24			
11/16/06	Klotz, Lynn			16:18-17:1			
11/16/06	Klotz, Lynn			24:8-25:3			
11/16/06	Klotz, Lynn			25:8-27:9	1 2		Def. FP 546
11/16/06	Klotz, Lynn			27:23-28:2			
11/16/06	Klotz, Lynn			28:12-32:12			
11/16/06	Klotz, Lynn			32:15-34:6			
11/16/06	Klotz, Lynn			34:12-35:24			
11/16/06	Klotz, Lynn			45:9-48:24	3 4		517 518
11/16/06	Klotz, Lynn						
11/16/06	Klotz, Lynn			51:3-52:2			
11/16/06	Klotz, Lynn			54:15-55:11			
11/16/06	Klotz, Lynn			58:16-59:4	6		802
11/16/06	Klotz, Lynn			60:5-61:3			

Depo Date	Witness	Hancock Designation	Abbott Counter Designatio	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
11/16/06	Klotz, Lynn			61:11-63:3			
11/16/06	Klotz, Lynn			64:2-69:24			
11/16/06	Klotz, Lynn			70:14-71:5			
11/16/06	Klotz, Lynn			71:16-72:15			
11/16/06	Klotz, Lynn			73:18-73:19	7		550
11/16/06	Klotz, Lynn			75:12-75:23			
11/16/06	Klotz, Lynn			76:4-77:10			
11/16/06	Klotz, Lynn			77:19-77:22			
11/16/06	Klotz, Lynn			78:1-78:21			
11/16/06	Klotz, Lynn			79:3-79:16			
11/16/06	Klotz, Lynn			79:20-79:23			
11/16/06	Klotz, Lynn			82:13-83:2			
11/16/06	Klotz, Lynn			83:10-83:13			
11/16/06	Klotz, Lynn			84:9-85:1			
11/16/06	Klotz, Lynn			86:11-86:18			
11/16/06	Klotz, Lynn			87:7-87:20			
11/16/06	Klotz, Lynn			88:18-89:7			
11/16/06	Klotz, Lynn			89:12-90:1			

Depo Date	Witness	Hancock Designation	Abbott Counter Designatio	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
11/16/06	Klotz, Lynn			90:13-91:3			
11/16/06	Klotz, Lynn			91:10-91:21			
11/16/06	Klotz, Lynn			95:5-100:12			
11/16/06	Klotz, Lynn			101:18-103:2			
11/16/06	Klotz, Lynn			103:13-103:23			
11/16/06	Klotz, Lynn			104:1-104:6			
11/16/06	Klotz, Lynn			105:14-105:23			
11/16/06	Klotz, Lynn			106:2-106:4			
11/16/06	Klotz, Lynn			106:8-107:12			
11/16/06	Klotz, Lynn			109:2-109:4	8		551
11/16/06	Klotz, Lynn			110:21-111:9			
11/16/06	Klotz, Lynn			112:13-112:22	9		803
11/16/06	Klotz, Lynn			113:1-114:20			
11/16/06	Klotz, Lynn			115:1-115:10			
11/16/06	Klotz, Lynn			116:1-116:7			
11/16/06	Klotz, Lynn			116:20-117:14			
11/16/06	Klotz, Lynn			119:8-119:22			
11/16/06	Klotz, Lynn			123:20-123:21	11		556

Depo Date	Witness	Hancock Designation	Abbott Counter Designatio	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
11/16/06	Klotz, Lynn			124:2-124:4			
11/16/06	Klotz, Lynn			124:24-125:22			
11/16/06	Klotz, Lynn			126:18-129:10			
11/16/06	Klotz, Lynn			135:2-136:3			
11/16/06	Klotz, Lynn			137:11-137:23			
11/16/06	Klotz, Lynn			138:10-138:11	12		559
11/16/06	Klotz, Lynn			138:13-139:6			
11/16/06	Klotz, Lynn			139:15-139:17			
11/16/06	Klotz, Lynn			141:15-141:24			
11/16/06	Klotz, Lynn			142:22-143:2			
11/16/06	Klotz, Lynn			143:23-144:6	13		561
11/16/06	Klotz, Lynn			144:10-144:17			
11/16/06	Klotz, Lynn			145:14-145:17			
11/16/06	Klotz, Lynn			145:24-146:16			
11/16/06	Klotz, Lynn			146:20-148:1			
11/16/06	Klotz, Lynn			148:23-149:9	14		804
11/16/06	Klotz, Lynn			149:13-149:18	15		805
11/16/06	Klotz, Lynn			149:22-150:19			

Depo Date	Witness	Hancock Designation	Abbott Counter Designatio	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
11/16/06	Klotz, Lynn			151:9-151:17			
11/16/06	Klotz, Lynn			158:11-158:21			
11/16/06	Klotz, Lynn			159:2-159:8			
11/16/06	Klotz, Lynn			159:12-160:1			
11/16/06	Klotz, Lynn			160:15-161:15			
11/16/06	Klotz, Lynn			161:21-163:3			
11/16/06	Klotz, Lynn			166:22-167:11			
11/16/06	Klotz, Lynn			170:2-172:5			
11/16/06	Klotz, Lynn			177:10-179:16			
11/16/06	Klotz, Lynn			180:4-184:12			
11/16/06	Klotz, Lynn			185:4-185:13	17		806
11/16/06	Klotz, Lynn			187:7-188:5			
11/16/06	Klotz, Lynn			189:3-189:20			
11/16/06	Klotz, Lynn			191:12-192:1	18		502
11/16/06	Klotz, Lynn			193:11-196:17			
11/16/06	Klotz, Lynn			197:4-198:2			
11/16/06	Klotz, Lynn			199:6-199:11			
11/16/06	Klotz, Lynn			200:2-200:12			

Depo Date	Witness	Hancock Designation	Abbott Counter Designatio	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
11/16/06	Klotz, Lynn			202:16-203:23			
11/16/06	Klotz, Lynn			204:4-205:2	19		807
11/16/06	Klotz, Lynn			206:13-208:5			
11/16/06	Klotz, Lynn			208:19-208:21			
11/16/06	Klotz, Lynn			208:23-209:16			
11/16/06	Klotz, Lynn			209:24-210:9			
11/16/06	Klotz, Lynn			211:6-211:12			
11/16/06	Klotz, Lynn			211:22-213:21			
11/16/06	Klotz, Lynn			214:3-216:23			
11/16/06	Klotz, Lynn			217:5-220:2			
05/16/07	Klotz, Lynn			229:24-231:19			
05/16/07	Klotz, Lynn			232:10-232:17			
05/16/07	Klotz, Lynn			234:18-237:17	20		808
05/16/07	Klotz, Lynn			238:10-239:2			
05/16/07	Klotz, Lynn			239:12-239:15			
05/16/07	Klotz, Lynn			242:6-242:24	21		809
05/16/07	Klotz, Lynn			243:7-243:15			
05/16/07	Klotz, Lynn			243:19-245:24			

Depo Date	Witness	Hancock Designation	Abbott Counter Designatio	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
05/16/07	Klotz, Lynn			246:16-247:4			
05/16/07	Klotz, Lynn			248:10-248:20	22		554
05/16/07	Klotz, Lynn			249:2-249:21			
05/16/07	Klotz, Lynn			252:21-253:11	25		810
05/16/07	Klotz, Lynn			253:16-256:2	26		511
05/16/07	Klotz, Lynn			259:22-259:24			
05/16/07	Klotz, Lynn			260:5-261:6	27		811
05/16/07	Klotz, Lynn			262:20-265:4			
05/16/07	Klotz, Lynn			265:21-266:16			
05/16/07	Klotz, Lynn			267:11-267:20			
05/16/07	Klotz, Lynn			268:11-270:20	28		L
05/16/07	Klotz, Lynn			271:2-271:7	29		M
05/16/07	Klotz, Lynn			272:5-274:1	30		H
05/16/07	Klotz, Lynn			274:18-275:7			
05/16/07	Klotz, Lynn			283:22-284:24			
05/16/07	Klotz, Lynn			288:9-288:16			
05/16/07	Klotz, Lynn			294:5-294:23			
05/16/07	Klotz, Lynn			297:24-300:8			

Depo Date	Witness	Hancock Designation	Abbott Counter Designatio	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
05/16/07	Klotz, Lynn			301:14-302:15			

Color Key to Deposition Designations

Designation by Plaintiffs

Counter Designation by Defendants

Designation by Defendants

Volume: I, Pages 1 - 224 Exhibits: 1 - 19

UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF MASSACHUSETTS

CIVIL ACTION NO. 05-1150DPW

- x

JOHN HANCOCK LIFE INSURANCE COMPANY,

JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY,

and MANULIFE INSURANCE COMPANY,

(f/k/a INVESTORS PARTNER INSURANCE COMPANY),

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

- x

VIDEOTAPED DEPOSITION OF LYNN KLOTZ, Ph.D.

Thursday, November 16, 2006, 9:10 a.m.

Donnelly, Conroy & Gelhaar

One Beacon Street

Boston, Massachusetts

Reporter: Dana Welch, CSR, RPR

Certified LiveNote Trainer

THE VIDEOGRAPHER: The court reporter today is Dana Welch of Merrill Legal Solutions.

Would the reporter please swear in the witness.

LYNN KLOTZ, Ph.D.,

having been satisfactorily identified by the production of his driver's license, and duly sworn by the Notary Public, was examined and testified as follows:

EXAMINATION

BY MR. WEINBERGER:

Q. Good morning. Could you please state your full name for the record.

A. Lynn Charles Klotz.

Q. And what is your current address?

A. Address? 5 Duley, D-U-L-E-Y, Street in Gloucester, Massachusetts 01930.

Q. Are you currently employed?

A. Self-employed.

Q. What kind of business do you have?

A. 90 percent of the time, I'm working on arms control policy, national and international arms control policy and biological chemical

weapons. These days, 10 percent of my time on consulting.

Q. And in the 90 percent of your time, are you working for clients?

A. No. I work -- I'm senior science fellow for the Center for Arms Control and Nonproliferation in Washington, D.C.

(Interruption for clarification by the reporter.)

THE WITNESS: They're an NGO.

Q. I have a host of questions for you about that that are much more interesting than the ones I want to ask, but I'll forego that.

A. Don't -- don't put me on my soapbox because I have a lot to say.

Q. And the other 10 percent of your time, you do consulting?

A. Yeah, these days, yeah. It was 50/50 before.

Q. Do you prefer Mister or Doctor?

A. Whatever you prefer. Doctor, I suppose.

Q. All right. Let's use that. You're a Ph.D., correct?

A. Yes.

Q. For what purpose were you -- were you looking at the Friedman report?

A. I think just general background.

Q. Is there anything in the report that you noted that you thought was incorrect?

A. No. I thought he did a very good job and thorough.

Q. Did you -- when was the last work you did for John Hancock as a consultant in connection with this investment?

A. The last work was on this investment. It was the interview with Dr. Leonard at Abbott. And I wrote up a preliminary memo on what -- what -- how the interview went and what was said.

Q. Okay. We'll be looking at that.

That was sometime in the -- in 2000, correct?

A. Yeah.

Q. And since then, you've done -- besides the preparation for this deposition, you've done no work on this?

A. Well, a year ago, I was retained by Choate Hall and Stewart to -- to look into some of the technical issues.

Q. What technical issues were you retained to look at?

MR. DAVIS: Objection. He's not -- we are not planning on calling him as a testifying expert. We have retained him as an independent consultant non-testifying; so work that he's done for us we would regard as work product.

So I'm going to instruct him not to answer questions about that work. He's certainly free to answer any questions about the work that he did pertaining to this transaction before he was retained as an independent consultant.

Q. All right. When -- when exactly were you retained; do you know?

A. I can't say exactly. I'm guess -- spring of 2000 would be my guess.

Q. I mean, in terms of the consultation -- strike that.

In terms of the retention by Choate Hall --

A. About -- about a year ago.

Q. About a year ago.

(Interruption for clarification by the reporter.)

(Off-the-record discussion.)

Q. And I -- and I know you know what I'm going to say, but you've got to wait.

The other thing is, is sometimes I pause --

A. Yeah.

Q. -- in the middle of a sentence because I want to get it right so that we have a clear record.

A. Okay.

Q. And that's not really an invitation for you to jump in and answer.

A. May have to remind me a few times.

Q. All right. We're not in a rush. It's not a speed contest.

The -- I think the question was, when were you retained by Choate Hall in connection with this case?

A. About a year ago.

Q. And about how much time have you spent on the matter?

A. About a year ago, I spent maybe two, three

weeks.

Q. If you could just answer this yes or no. Did you prepare any -- anything in writing in connection with this --

MR. DAVIS: Objection. I don't think that -- I instruct him not to answer that question.

I mean, again, he's not a testifying expert, so I don't think you're entitled to inquire on work that he's done in a non-testifying basis.

MR. WEINBERGER: Well, yeah, I -- I understand. But I -- I think that because he is a percipient witness, I'm at least entitled to, without getting into the substance of the work, to test whether that's -- you know, it's a legitimate claim or privilege by asking about the existence of things without going into the substance, I think I'm entitled to do that.

MR. DAVIS: No, I don't think you are. We've disclosed the fact that we retained him as a non-testifying expert. And actually, I don't think you're entitled to any more than

A. Yeah. All right.

Q. Let -- let me just rephrase.

A. Up to that point. Okay.

MR. WEINBERGER: Thank you, Brian.

Q. Other than the contact you had about documents --

A. Uh-huh.

Q. -- in between the time of your interview with Dr. Leonard and Mr. Blewitt and your retention as an independent consultant in this case, did you have contacts with anybody at John Hancock about this litigation?

A. No.

Q. Did you have any contacts with Mr. Blewitt about anything?

A. Yes, shortly after the Leonard interview. Not verbal, but I sent him an e-mail which was the summary of the e-mail.

Q. I see.

A. And that was it.

Q. And that was it?

A. Yes.

Q. And that was the last time you spoke to Mr. -- and was that the last time you spoke to

Mr. Blewitt until you became -- you were retained as an independent consultant in this case?

A. Yes.

Q. All right. When were you first retained by John Hancock in connection with the investment -- well, let's strike that. Let's make sure we're clear.

You -- you're -- you're familiar with the investment which is the subject of this litigation, correct?

A. Yes.

Q. And you -- you were retained by John Hancock as a consultant in connection with evaluating that investment?

A. On the technical end, not on the dollars end.

Q. All right. When were you retained by John Hancock in connection with this?

A. Spring of -- spring of 2000. And I don't remember exactly.

Q. Okay.

MR. WEINBERGER: Let's mark as Klotz Exhibit 1 a document dated May 1, 2000; appears to be a draft or a letter from Lynn Klotz to John Hancock Life Insurance Company.

(Exhibit No. 1, JH 001691 - 001693, marked
for identification.)
Q. Dr. Klotz, this appears to be a proposed
consulting or confidentiality agreement --
A. Uh-huh.
Q. -- that you proposed to John Hancock; is
that correct?
A. Yes. Their language, so they probably
sent it to me in that form.
Q. And do you know if this was in connection
with the investment transaction which is the
subject of this litigation?
A. I assume it would be, yes.
Q. So that helped place the time -- time
frame in which you began this work?
A. Yes.
Q. Roughly May 2000?
A. Yes.
MR. WEINBERGER: Let me ask the reporter
to mark as Klotz Exhibit 2 an e-mail dated
June 2nd with an attached document.
(Exhibit No. 2, JH 003089- 003100, marked
for identification.)
(Off-the-record discussion held.)

Q. Okay. Have you had a chance to look at Klotz Exhibit 2?
A. Oh, you want me --
Q. All right. So the first page of Klotz Exhibit 2 appears to be an e-mail that you sent to Mr. Blewitt --
A. Uh-huh.
Q. -- on June 2; is that right?
A. Yes.
Q. All right. And in that, you attach your CV. Is the attachment --
A. Yes.
Q. You definitely need to -- to wait until I finish. People think that it speeds up the deposition, but in fact it -- it really winds up taking a lot more time.
MR. DAVIS: Please wait until he finishes the question and then you answer.
THE WITNESS: Yes.
MR. DAVIS: Thank you.
Q. All right. So then I have to go back and think about what I was going to ask.
It states that attached is a CV. Is the attachment a CV of yours that was current as of the

time frame of June 2000?

A. Yes, it is.

Q. All right. Now, in the e-mail, you refer to an idea of -- Mr. Blewitt's idea about financing baskets of drugs combined with options to convert to stock targeted to companies of sufficient size --

(Interruption for clarification by the reporter.)

MR. WEINBERGER: Let me -- let me rephrase.

Q. The e-mail refers to a concept of financing baskets of drugs and goes on to state some other attributes. Was that something that Mr. Blewitt had raised with you?

A. Yes. The basket of drugs, I remember. The rest of the sort of thoughts about business structure, I don't remember. But I wrote it and he must have phrased it to me or something like that.

Q. Has this -- was this an idea that you had not previously had experience with?

A. We --

MR. DAVIS: Objection. You may respond.

THE WITNESS: We -- yeah, we did discuss.

I was trying to -- because I had done a couple of shorter consulting projects for him and I was trying to understand what he was thinking of in terms of investment strategies. So we had had some discussions. And one of the things I definitely remember is that he made the comment, and I've heard this from other financial types before, is that you have to do this much work investing in a company that's worth $10 million as one that's worth $100 million, so you might as well just think about big investments. So I knew he was hunting for bigger things.

Q. Why is that, because of the due diligence requirement?

MR. WEINBERGER: Objection. You can respond.

THE WITNESS: No. I just -- I think -- I mean, obviously, I'm assuming -- well, let me answer it from my side, not his because I can't assume what he was thinking. It's just that if you do a lot of work and you're a big financial company and you have lots of money that you are supposed to invest, that you

should look for larger investments. And that was my take on it.

Q. So, in other words, the concept of financing baskets of drugs would -- would lead to a bigger investment?

A. It likely would. It also had a lot of other attributes I liked, especially because it was Abbott.

Q. And what attributes were those?

A. Well, small biotech companies are risky from about every point of view. I mean, I can go into that at some point if you want. But large pharmaceutical companies know how to go through discovery and through development into the marketplace, so it'd be a less risky kind of investment relative to biotech companies.

Q. Had you had experience with the R&D development by large pharmaceutical companies before?

A. No. Mostly -- not before. Mostly small biotech companies, startup companies, lot of experience there.

Q. So what experience, if any, did you have with the R&D process of large pharmaceutical

companies as of June 2000?

A. My main experience was what I learned in preparing to teach my course on biotechnology and modern drug discovery and development.

Q. Which was when?

A. I taught that course three times. It was once to graduate students at Harvard Extension and twice in the Harvard Extension School Summer Executive Program. It was titled something like that, which was a three-day -- that was a three-day -- two, three-day versions two years.

Q. Okay. And what years?

A. Late '90s.

Q. All right. And other -- other than that, you did not have -- did you have any experience with large pharmaceutical companies, R&D process or drug development?

A. I -- I would say just an academic experience. I wasn't involved in any projects. I mean, obviously since small biotech companies license the big companies, I had to be aware of the way the companies were thinking.

Q. Let's look at the attachment, the CV.

A. Uh-huh.

Q. Actually, rather than go through this, if you could just state for me chronologically so we have this in one place, just a chronological brief history of your educational and employment and consulting experience up to the present day, that would be very helpful.

A. Sure. I can do that.

I got my bachelor's degree in mathematics at Princeton in 1965. I was a graduate student and professor of Bruno Zimm's lab. If you were a chemist or a microbiologist, you would know him as a fairly famous physical chemist.

(Interruption for clarification by the reporter.)

THE WITNESS: Let me even back up. I got my bachelor's degree in '65 at Princeton. I worked for one year after that in the laboratory of Jacques Fresco, J-A-C-Q-U-E-S, Fresco at Princeton. I had worked in his laboratory through undergraduate school and before undergraduate school had published a number of papers with him. So I worked for one year after undergraduate school. Then went to graduate school at University of

California, San Diego. And I actually was focusing on Bruno Zimm to be my Ph.D. advisor; he did become my Ph.D. advisor. Got my Ph.D. in 1971 in chemistry and went straight then to Harvard junior faculty. That was unusual in the sense that most people post-op for a while before they actually get a faculty position. But I had skill or luck to have a thesis that was very highly regarded, and so I went straight to Harvard as an assistant professor. An assistant professor there for four or five years. And I can't remember exactly when, but I got promoted to associate, which at Harvard is non-tenure. After my eight years, I suffered the fate of most Harvard junior faculty who aren't tenured, you have to go look somewhere else. And in the process of that, I ran into some people and some of my ex-students and we started a biotechnology company, so I got out of academia and got into the business development end of biotechnology.

Q. Was that BioTechnica?

A. BioTechnica International, yeah.

Q. Okay. Keep going.

A. Oh, keep going.

I was at BioTechnica maybe for eight years. The title kept changing, but the work was the same. I think one title was vice-president of scientific planning, then it was vice-president of new business development.

MR. DAVIS: I think, Dr. Klotz, you have to slow down a little bit.

THE WITNESS: Okay.

MR. DAVIS: You -- you don't want to wear out the stenographer by 10:00 a.m.

THE WITNESS: At BioTechnica, I had several titles, they all pretty much amounted to the same thing, which was new business development for that company. In that role, I founded two spin-off companies. One was BioTechnica Diagnostics, which was a joint venture with Forsyth Dental Research Institution in Boston. Forsyth is one of the preeminent dental research institutions in the country and probably in the world. And we spun off a diagnostics company to use DNA probes, one of the early DNA probe diagnostic companies to do periodontal disease

diagnostics. So I did the business strategy,
the business plan, the market project --
projections, the value, the company, the whole
works.

Q. So -- so your work in BioTechnica was --
is it fair to say was from the business end as
opposed to the product development end?

A. Both.

Q. Both.

A. Yeah. Product development I would
character -- characterize as part -- part of the
business end. So, yes, I was on the board of
directors, too, as I was a founder.

Q. Were they focused on diagnostic products?

A. No. That was just the subsidiary,
BioTechnica Diagnostics. The main company was
focused on using then what was the state-of-the-art
bacterial genetic engineering to do chemicals,
chemicals manufactured through genetic engineering.
And agriculture, we had -- 50 percent of our focus
was on agricultural biotechnology.

Q. Did -- did they do any work in
pharmaceuticals?

A. No.

was VP of research for all the companies. I was
sort of his right-hand outside person and I was
aware of -- of almost all the new businesses that
they were thinking of and was involved in one way
or another.

MR. DAVIS: While we're -- I'm sorry to
interrupt.

(Off-the-record discussion held.)

Q. All right. Let's look at the second page
of your CV.

A. Uh-huh.

Q. Exhibit 2. Up on top, it says examples of
recent biotechnology related --

A. Uh-huh.

Q. -- activities. Do you see that?

A. Yeah.

Q. The second one says, "Evaluated for a
major investment bank, a company's technology,
competitor's technology, intellectual property and
regulatory aspects of properties."

Who was that work for?

A. That would be Hancock. And I presume,
since I wrote this a whole while ago, I presume
they wanted Jay George and me -- this is after

Oncor went out of business; Jay George and I worked together for a short period of time. They wanted us to evaluate the status of cancer research, cutting edge therapies, where these therapies were going to go, what therapies looked promising and which ones didn't look promising. And we did that for Hancock.

Q. And what was the purpose of that?

A. They had made an investment in a company which was a cutting edge company that -- that was doing drug discovery in the area of apoptosis, which is programmed cell death which is involved in cancer.

Q. And do you remember what the company was?

A. I don't remember the name, no.

Q. The investment had already been made before you became involved; is that correct?

A. Yes, I think so.

Q. So what was the --

A. I should say I think so. I don't know.

Q. What was your understanding of the purpose of your consulting with them?

A. Well, I think they just wanted to know where things were going to be five or ten years

down the road because that was sort of the time frame we were doing that study.

Q. And do you have a recollection of when this prior work for Hancock was?

A. No. It was a few years before, I think, but I couldn't pin it down.

Q. Let's see if we can pin it down a little.

MR. WEINBERGER: Let's mark this as Klotz Exhibit 3, a letter dated August 29, 1998 and a draft consulting agreement.

(Exhibit No. 3, Draft Consulting Agreement, marked for identification.)

MR. WEINBERGER: And I'm going to mark as Exhibit 4 a letter from Dr. Klotz to Steve Blewitt and Dana Donovan, September 9, 1998 and craft consulting agreement.

(Off-the-record discussion held.)

(Exhibit No. 4, JH 001694 - 001698, marked for identification.)

BY MR. WEINBERGER:

Q. All right. So if you look at Exhibit 4 and 5, do they appear to be -- are -- are they communications that you sent to Steve Blewitt?

A. Okay. I have a 3 and a 4 here.

Q. 3 and 4.

A. Okay.

Q. Concerning consulting work that you were asked to undertake for John Hancock?

A. Yes, 3 certainly is.

Let me look at 4. Yeah, it's the one with Jay George; that's the only one the two of us did together, yes.

Q. Is there a reference to Jay George here?

A. Yeah. He's in the -- he's in the consulting agreement, Gaithersburg, Maryland.

Q. I see. So -- so -- in other words, he was also going to consult --

A. Yeah, we were -- we were working together on this one for Hancock.

Q. And so would this refresh your recollection as to the time frame of your prior work for Hancock?

A. Well, I just -- I wouldn't say it refreshes my recollection. I knew it was a few years prior, and this is a date that's a few years prior, so --

Q. Okay. And other than this project, had you done any other work for John Hancock until

THE WITNESS: I don't want to challenge you on that one.

Q. Okay. So the work that you just described involving SangStat, was that in between the work you did on the -- the cancer consultation and the work you did on this transaction that's the subject of this lawsuit?

A. That is my recollection. I can't say for sure.

Q. Did you generate any -- any written analysis in connection with that work?

A. Again, I don't remember, but I presume I did.

Q. Did you generate any written analysis in connection with your -- your work in 1998 for John Hancock?

A. Yes.

Q. And what was that?

A. It was a long report.

Q. This was a report with respect to these cancer drugs that were in development?

A. Yes. Well, in discovery mostly.

Q. In discovery?

A. Yeah. A few may have been in development,

but it was mainly looking to the future what might be exciting or might not be exciting.

Q. Now, this third bullet on your resume says, "Determine the likely status in the year 2005 of drug discovery and development in the major therapeutic area for a major investment bank."

A. Let me see what this says. "Determine likely status of the drug discovery and development." That must be -- the third one must be the one on the cancer.

Q. All right. So then what would the second one be?

A. And two, I don't remember what that was.

Q. Was it --

A. Oh, likely status in the year 2005 --

Q. Correct.

A. -- of drug discovery and development in the major therapeutic area. I don't know. 2005? I mean, that's --

Q. I think it's saying, my interpretation is you're determining at some earlier date the likely status in the year 2005?

A. Oh, yes, right, yes, exactly. So that would be the Hancock cancer status project, yes.

this transaction?
A. No recollection.
Q. Okay.
A. I don't think I did. I don't think I did.
Q. The reference to "Wrote business plans for first and second stage financing," can you tell me what that refers to?
A. Yeah. The first stage would have been the two Codon -- first and second, because Codon had first stage financing. The second stage financing probably would have been the small molecule drugs, but that business plan didn't get completed.
(Interruption for clarification by the reporter.)
Q. Now, other than what we've talked about, had you -- have you engaged in -- up -- up until the work you did for Hancock in 2000, did you engage in any consulting -- consulting with respect to the -- the development prospects of any pharmaceutical compounds in connection with a potential investment?
A. Of pharmaceutical compounds?
Q. Pharmaceutical compounds.
A. In other words, not discovery stage, but

things that are further along?

Q. No, no. Including discovery stage, but related to pharm -- a potential pharmaceutical compound.

A. Yes.

Q. Okay. Can you identify what that work was?

A. That would be the Codon oligonucleotide drugs.

Q. All right.

A. And also the Codon small molecule drugs.

Q. All right. And we talked about that?

A. And we talked about those.

Q. Anything we haven't talked about?

A. No, not -- well, there might be, but I -- you know, I just don't remember everything I did in my consulting career.

Q. But sitting here today, you can't recall anything else?

A. No, I can't recall anything right now, no.

Q. Okay. Do you consider yourself an expert with respect to any particular types of pharmaceutical compounds?

A. Yeah, oligonucleotides.

not sure if I did some other small project in there or not. I don't recall.

Q. Were you involved in any way in a project involving Idun, I-D-U-N, Pharmaceuticals in La Jolla?

A. I'm guessing that was the apoptosis company whose name I don't remember. I do remember they were in San Diego.

Q. Apoptosis being...

A. Programmed cell death. It was the cancer company that they had invested in.

Q. I see.

And was Abbott Laboratories involved in that program?

A. Not to my knowledge.

MR. WEINBERGER: Let's mark as Exhibit 6 a document entitled Purchase Recommendation dated March 24, 1999.

(Exhibit No. 6, JH012355 - 012367, marked for identification.)

Q. Do you recognize this document?

A. No, I don't.

Q. Over on page 5 of the document, it refers to Abbott agreements. Talks about a collaboration

between Idun and Abbott to discover and develop small molecule cancer therapies that target the apoptosis pathway; is that correct?

A. That's what it says.

Q. So would this indicate to you that this is this agreement that you were looking at in connection with the cancer project?

MR. DAVIS: Objection. You can respond.

THE WITNESS: The answer is no because Jay George and my job was to look at the cancer therapy field. Steve specifically said -- Steve Blewitt specifically said the investment's already been made. He was more interested in cancer five to ten years down the road.

Q. Well, if you look at this, it says March 24, 1999, correct?

A. Uh-huh.

Q. And the consulting agreement you sent to Mr. Blewitt that we looked at earlier was in 1998 --

A. Uh-huh.

Q. -- correct?

And that was in connection with the cancer

apoptosis work, correct?
A. Uh-huh.
MR. DAVIS: You have to respond verbally.
THE WITNESS: Oh. Yes.
Q. And if you look over at page 12361, that's the Bates number, it's page 7.
A. Uh-huh.
Q. It states, "John Hancock commissioned two consultants to review the field of anticancer therapies to project the importance of various cancer therapies in five years." Then below, middle of that paragraph --
A. Uh-huh.
Q. -- it says, "Dr. Lynn Klotz of Harvard and Dr. Jay George have concluded," et cetera.
A. Yes.
Q. Do you see that?
A. Yes.
Q. So would this indicate to you that the work you did was not in connection with a completed transaction but in connection with a transaction that Hancock was considering?
A. Yeah, this document --
MR. DAVIS: Please pause for a moment.

Objection. You may respond.
THE WITNESS: Yeah, that's what this document indicates to me.
Q. So that does not refresh your recollection at all?
A. That was not my understanding.
Q. So it was not your understanding that you were involved in potential due diligence with respect to this transaction?
A. No.
Q. All right. Now, was it Mr. Blewitt who approached you in 2000 to be involved in the transaction with Abbott Laboratories that we are here talking about?
A. Yes.
Q. Okay. And what did -- what did he tell you at that time about what he wanted you to do?
A. Well, I can't remember exactly what he told me when; but at some point, he told me about the basket of pharmaceuticals. I liked the idea very much.
Q. What did he tell you about the basket of pharmaceuticals?
A. Just -- I think just in general, again, I

can't remember when I got the specifics, but in general, that they were thinking of licensing a basket of pharmaceuticals from Abbott. And the reason I liked the idea is because I thought it fit my understanding of what their strategy was and it seemed like a good strategy.

Q. So what -- what was it they asked you to do in connection with this transaction? To -- and could you be as -- as specific as memory would allow.

A. Yes. We decided early on on a strategy. We had the Abbott memoranda which put us way ahead of the game on all the drugs. I studied those carefully, and we decided our strategy would be through brief -- well, through literature search at the abstract level and through interviews with experts in the field who were also identified from the literature search to just make sure that the Abbott -- the Abbott memoranda on the -- on the basket of drugs was consistent with what we were finding out in the field. In other words, verifying that the Abbott memoranda were consistent with what we found out.

Q. When you say the Abbott memoranda, are you

talking about descriptive memoranda --
A. The descriptive memoranda of everything in the basket.
Q. You need to wait -- you need to wait until I finish the question because --
A. Uh-huh.
Q. -- it's just -- it's just going to require me to repeat everything.
A. Yeah. No, I -- I understand that.
Q. Okay. Now, again, I've got to go back and figure out --
MR. DAVIS: I -- I agree with you, Jeff, he -- he shouldn't be speaking over you, but I think we know why he shouldn't be speaking over you.
Please, Dr. Klotz --
THE WITNESS: Yes.
MR. DAVIS: -- let Mr. Weinberger finish his questions before you respond.
MR. WEINBERGER: Again, I know that nobody is doing anything intentionally and I appreciate your attorney's insistence in this; he's being very helpful. We just want a clean record.

MR. DAVIS: I agree.

Q. So the question is -- oh, yes, the question -- the question is, when you say Abbott memoranda, are you talking about documents called descriptive memorandum with respect to each proposed compound in the basket that Abbott prepared and supplied to Hancock? Is that the document you're talk -- document you're talking about?

A. Yes.

Q. You were given those documents sometime in mid-2000; is that correct?

A. Yes.

Q. With respect to, at least at that time, the compounds that were being looked at, correct?

A. Yes.

Q. And why -- did Mr. Blewitt explain why -- why the -- the information in those compounds needed to be verified, checked for consistency with literature and experts?

MR. DAVIS: Objection. You can respond.

THE WITNESS: Okay. I think just as part of the due diligence or that part of the due diligence, yes.

Q. What do you mean by due diligence?

A. To make sure that what Abbott was saying was accurate.

Q. Why couldn't you just accept what Abbott was saying?

MR. DAVIS: Objection. You can respond.

THE WITNESS: Yeah. I think -- I think we -- we assumed they were accurate, but we wanted to make sure there were no red flags, that in fact what they were saying was what the outside world -- was consistent with what we could find out in the outside world.

Q. Why?

A. Hancock --

MR. DAVIS: Objection. You can respond.

THE WITNESS: Okay. Hancock was about to make a sizeable investment.

Q. Was that the whole answer?

A. Well, it's just standard due diligence, too.

Q. It wouldn't have been wise just to rely on what the -- Abbott was saying without any more in your view, correct?

MR. DAVIS: Objection. You can respond.

Q. In terms of the standard of practice that you just referred to?

MR. DAVIS: Objection. You can respond.

THE WITNESS: Yeah. I mean, I think -- I think our view was that -- that Abbott -- what Abbott was telling us was accurate, but we were obligated to confirm that.

Q. Okay. And in fact, at the -- at the end of your process, you did conclude that what Abbott was telling you was accurate, correct?

A. Yes.

Q. Now, what -- what are the -- we've talked some about your qualifications and your background. What qualifications of yours did you believe were most important to performing this assignment?

A. Well, I have a very general and wide background in basic science through at least understanding, being aware of what the drug development issues are and marketing issues as well. So I think that this very broad background, given that this was a very broad basket of drugs, was a useful background for this particular assignment.

Q. Okay. Any other particular qualifications

that you believe were relevant to this assignment?

MR. DAVIS: Objection. You can respond.

THE WITNESS: Yeah, I think that's pretty much it. I have a strong academic background, had gone into business, so I understood business, I understood markets, I understood to some extent clinical trials, the clinical trial process. I certainly understood -- understood what issues might come up. So I think it was just the background.

Especially in some of these drugs, like the cytostatic drugs were cutting-edge drugs, and this is the kind of thing that goes back to basic molecular biology and again, I had awareness of a lot of these issues.

Q. Now, you mentioned clinical trial process. Could you -- could you tell me the experience you've had in the clinical trial process?

A. Again, a lot of this comes from my teaching. I certainly understood the phases of clinical trials, I understood how many patients were involved, I understood the costs and the timelines for getting through these phases. I understood what kinds of drugs got through more

easily, depending on clinical trial end points and things like that. I think in general I really understood the clinical trial process, but not the particulars of how doctors get recruited and things like that.

Q. All right. But you -- you were comfortable enough with the clinical trial process to take on this assignment that involved to some extent having an understanding of how that process works with respect to --

A. Yes. We're also relying on the Abbott descriptive memoranda because when things are in clinical trials, what's going on is not public. So there, we relied very heavily on the Abbott descriptive memoranda. And their descriptive memoranda and some of the things we found out did bring up some questions, which in Dr. Leonard's interview we asked.

Q. So, in other words, to the -- to the extent that information in the descriptive memoranda gave rise to questions, you understood that you had the ability to go to Abbott and get more information and follow up on that?

MR. DAVIS: Objection. You may respond.

Q. Is that right?

A. Yeah. I -- I don't think I saw the need to go to Abbott. We interviewed Dr. Leonard on the telephone.

Q. If you needed more information, did you understand that you had the ability to ask for that?

MR. DAVIS: Objection. You may respond.

THE WITNESS: Yeah, I understand I had the ability. I would not ask for it; probably Steve Blewitt would.

Q. Okay. And you didn't -- I think you said you -- you decided you didn't have to ask for more information; is that correct?

A. I think Steve was satisfied with the stuff I prepared for him, the interview with Leonard.

Q. Satisfied in the sense that he didn't need to go back and get additional information from Abbott?

A. You would have to ask him that. I can't answer that.

Q. But that was your understanding?

MR. DAVIS: Objection. You may respond.

THE WITNESS: That's what I felt, yes.

Q. Well, did you feel, based on your investigation, that you needed to get other information from Abbot?

MR. DAVIS: You talking about at the conclusion of his work?

MR. WEINBERGER: Yeah.

THE WITNESS: Well, I knew he had other people working on the project as well, so it was hard for me to assess what additional information might be needed.

Q. Well, on the scientific end, was there anybody else working on this project?

A. I don't know.

Q. So in terms of your conclusions, putting aside what someone else may have had, I'm asking about you, did you conclude at the conclusion of the product that you didn't need any additional information from Abbott?

A. Well, given our strategy to confirm the descriptive memoranda, we pretty much did that, we did that.

Q. Okay. So my question is, did -- did you conclude at the end of your process that you didn't need any further information from Abbott?

A. In terms of that strategy, yes.
Q. How much time did you spend on this project?
A. Oh, that would be in the invoices. I'm thinking about half time for a couple of months.
Q. Well, I don't know what your full time is. So if you could give me an estimate.
A. Oh, you know --
Q. It's probably different than -- than lawyers is my guess.
A. I mean, this is a little bit of a guess. 20 hours a week for a couple of months.
Q. Okay. So your best estimate, understanding it's imprecise, would be --
A. Month's full time or something, yeah.
Q. 40 hours or was it 80 hours? 80 hours?
A. Yeah. Well, let's see, 20 hours a week, four weeks, 80 -- maybe over a hundred hours.
Q. A hundred hours?
A. Yeah.
Q. Okay. Now, you mentioned that part of the approach was to look at literature, correct?
A. Look at abstracts in the literature.
Q. And part of the approach, I think you

said, was to talk to experts in the field?
A. Yes.
Q. Okay. Where did you propose to get the names of experts to talk to?
A. I got the names from scanning the literature, seeing who was publishing the most and the most interesting papers and identified them from there.
Q. From the literature?
A. From the literature.
Q. And then cold-called them?
A. Yeah. Usually called their secretary and asked to set up an interview.
Q. Were they paid?
A. Yes.
Q. By -- by you?
A. Well, I -- I wrote the check and Hancock reimbursed me.
Q. Okay. How much were they paid?
A. I think $250 for a half hour. It could have been 200, but something like that.
Q. I assume you were paid for this job?
A. Yes.
Q. What was your fee arrangement?

A. It's hourly. And either 200 or 250, I just don't remember.

Q. And that's -- that's how you were paid; at -- at the -- at the conclusion, you were paid on an hourly basis?

A. I think I probably wrote an invoice every month and then got paid monthly.

Q. Okay. There was no other compensation involved besides your hourly rate?

A. No, nothing.

Q. Okay. I'm not implying anything. I just need to ask --

A. No, no.

Q. -- some of these questions.

A. I -- I understand. I understand.

Q. All right.

(Off-the-record discussion held.)

(Exhibit No. 7, JH 003080 - 002090, marked for identification.)

Q. All right. Let -- let me first ask you, is this one of the documents you reviewed that refreshed your recollection that we talked about earlier this morning?

A. Yes.

MR. DAVIS: -- before you begin to answer.

THE WITNESS: Sorry.

MR. DAVIS: Sorry. Picking up where we were.

Q. Do you have the question in mind, sir?

A. No.

Q. The question is this: Was this the first work product that you did in connection with the transaction with Abbott?

A. I expect it was from the date and from the content.

Q. Okay. And can you tell me what this document is?

A. Well, from the looks of it, I looked over what was in the basket of drugs, presumably read the descriptive memoranda at that point, although my memory doesn't tell me one way or another, and this was my first take on what was in the baskets.

Q. Based on some of the statements in here, would it -- would it be a fair assumption that you had read the descriptive memoranda before you wrote this?

A. It would be a fair assumption, yes.

Q. All right. The first -- the first heading

says General Thoughts, Ideas and Questions.

(Interruption for clarification by the reporter.)

Q. All right. And then it says, "The basket is really two baskets."

A. Uh-huh.

Q. Can you tell me what you meant by that?

A. Yeah, in general I can. There are a number of cytostatic drugs in that basket. From my point of view at that time, that cytostatic drugs all had a number of issues which were identical. They were new to the FDA; it was unclear about how one would measure clinical end points that would satisfy the FDA because they were new. And because of the type of drugs, they didn't cure anything; they just -- they just stopped something from -- from -- from spreading or -- or getting worse, cancer from spreading or getting worse, metastasizing. And since I thought there were a lot of general issues and that this project was not going -- didn't have an infinite end point, time end point on it, that we ought to treat, at least as a first take, all the cytostatic drugs in one basket, those are the common issues, and that the

rest had to be treated separately because they were all very different.

Q. Okay. So in looking at the risk, were you saying that there could be risks that would be common to all the cytostatic agents regardless of the particular merits of the --

A. Yes.

Q. -- individual compound?

A. Yes. And I think mainly a clinical trial risk and FDA risk, yes.

Q. So that might make these drugs -- might mean that they should not be evaluated independently, each one on their own, but to some extent as a group?

A. Well, as a first take, look at them as a group. Then the next step would be to see where they are in the development process, and then you would evaluate them independently.

Q. All right. Now, if you look at pages -- page 5 of the document --

A. Uh-huh.

Q. -- summary profile of the basket.

MR. DAVIS: I'm sorry. What page?

MR. WEINBERGER: 5.

Q. There's a chart of compounds. Was it your understanding that these were the compounds that at the time, that is, June 2000, were being proposed as the basket for the Hancock investment?

A. Yes, that was my understanding.

Q. And could you tell me which of those were in this category of cytostatic agents?

A. Well, ABT-627; ABT-518, the FTI simply because I see my note there that says, "same as Abbott 518 and urokinase inhibitor, same as Abbott 518"; that's referring, I think -- I think to the fact that they are cytostatic drugs.

Q. Okay. Going back to the first page --

A. Uh-huh.

Q. -- you say, "Some of the drugs in the basket are well along the clinical trials and represent new but more traditional approaches to diseases. In contrast, the remaining drugs are cytostatic cancer agents for cancer. And since this is a new untried strategy for everyone, it is high risk."

A. Now, where are you reading this? I --

Q. This is the second sentence on the first page of the analysis.

A. Oh, okay, second sentence -- oh, second sentence. In contrast, yes.

Q. "In contrast, the remaining drugs are cytostatic cancer agents for cancer. And since this is a new untried strategy for everyone, it is high risk."

A. Yes.

Q. Was that your assessment as of this time period, that the cytostatic cancer agents in the basket were high risk?

A. Yes.

Q. And that included 518?

A. 518 was -- let me just look at the notes, make sure that the numbers -- oh, yeah, 518 was already in clinical trials, so that would be less high risk.

Q. Well, if you look at the chart, the 208, on page 5.

A. Uh-huh.

Q. Under preliminary assessment promise/market risk, under ABT-518 under market risk, someone has written "high"?

A. I -- I -- that's my table, so I wrote it.

Q. Okay. So you'd agree that it was your

ever found out the answer?

A. I don't recall that I ever got the answer, but I may have. It's a long time ago.

Q. Okay. If you look over at page 2 --

A. Uh-huh.

Q. -- you ask the question, "How do we value the technical aspects of the drug aspect in competitive drugs?" Do you see that?

A. Now, where is this? Oh, yes. How to evaluate the technical aspects of the drug basket and competitive drugs.

Q. Right.

And the last sentence, you say, "From the point of view of due diligence, experts should be retained for most of the drugs."

A. Yes.

Q. Correct?

A. That's what I said there. We end -- we ended up interviewing experts, not retaining them.

Q. Well, why did you believe from the point of view of due diligence experts should be retained for most of the drugs?

A. Well, it'd be -- obviously, it would be useful to have expert opinion on the drugs. And in

the end, for time reasons, we decided that we would
just interview experts once we identified them.
Q. Why did you feel it would be useful to
obtain experts for most of the drugs?
A. Well, it's all -- it's almost like a
throwaway statement. Well, gee, we have all these
drugs; I know something about all of them, but I
can't claim to be an absolute expert in any of the
fields, so perhaps we should retain experts.
Q. But at the minimum, you felt it was
advisable to talk to experts?
A. Certainly at the minimum advisable to talk
to experts.
Q. And why did you believe that?
A. Well, because I -- I have to back up and
say this maybe more generally.
I said a little bit earlier that I'm aware
of almost all aspects from basic research through
marketing drugs through my sort of business and
academic experience. Aware is not knowledgeable.
The next step is knowledgeable. If you're aware of
something that you better get knowledgeable about,
you get knowledgeable. And I would characterize
getting knowledgeable over a period of a month or

two about something would put you in the 90 percent category, you probably know 90 percent of everything that's going on. But the last 10 percent is what experts know. Because they've been in the field for a long time, they're the ones who think about things all the time; they're the ones that have that sort of 10 percent of mostly unpublished knowledge, I would say.

Q. Okay. Now, under the heading How Do We Value Sales of the Drug Basket, you say, "Abbott's sales estimates are likely all high because they would need to be optimistic to sell the drugs/programs internally."

Now, can you tell me what you meant by that sentence?

A. I know that from my own experience in biotechnology companies and from reading outside reports, people are doing reports on industry, people tend to -- tend to make sales estimates that are high. And that was just a -- as -- as I said earlier, I was not involved in any of the financial end; but as a consultant, I always feel obligated to -- to make statements if I think they might be useful to the client, even if it's something I'm

not involved in.

Q. And why did you believe the -- for what reason were the sales estimates generally high in your experience?

MR. DAVIS: Objection. You can respond.

THE WITNESS: Yeah. It's -- I mean, almost every business plan from a biotech company, almost every report from these companies that do -- do reports that they sell for 2- or 3,000 bucks, the cases where I've had access to those reports and I've done my independent sales estimates, they always turn out to be high. Almost always, I can't say always for sure.

Q. So were you communicating to Hancock that they should not just blindly rely on --

A. Yes, that -- that's pretty much all I was --

Q. Let me finish the question.

MR. DAVIS: Let him finish his question.

THE WITNESS: Okay.

Q. So were you communicating to -- to Hancock that Han -- that it should not blindly rely on Abbott's sales projections, but do some due

diligence of its own to determine appropriate amounts?

MR. DAVIS: Objection. You may respond.

THE WITNESS: I was certainly indicating that they should not rely on Abbott's sales estimates. I probably was not suggesting they should do due diligence on their own because that was not my problem -- project on that.

Q. You say in that next paragraph -- well, strike that.

Then you give -- you put forth some ideas to Hancock for estimating sales right below that, correct?

A. Uh-huh.

Q. Is that right?

A. Let me see, estimating actual sales -- okay. Yeah, I was just giving him -- just throwing out some ideas.

Q. Now, under Number 1, am I correct that you're suggesting one approach would be to determine dollar sales for a number of top drugs in each therapeutic area and then average the sales of drug in that area?

A. Uh-huh.

Q. Is that yes?

A. Yes.

Q. You have to say yes or no --

A. Yes, I know.

Q. -- because uh-huh is ambiguous.

A. Yes.

Q. All right. Now, in that connection, you say, "Cancer and antibiotic markets" -- I'm sorry -- "Cancer and antibiotic markets are highly fragmented, so the average sales of a particular drug is likely small, perhaps less than 100 million," end quote. Is that your understanding?

A. I would say that was probably my guesstimate. I mean, the first part of that statement is -- is absolutely true. I mean, there are many cancer drugs out there, there are many antibiotics out there. A lot of the antibiotics are just slight modifications on the other antibiotics, and the -- the markets for an average drug is -- are fairly small.

(Interruption for clarification by the reporter.)

Q. You then say, "The average sales of the top five drugs may also be less than 500 million,

less than half of Abbott's projected sales." Do you see that?

A. Yes.

Q. What -- what projected sales were you referring to there?

A. They were either in the descriptive memoranda or -- or somewhere because I obviously had copies. I'm -- I'm thinking they were in a descriptive memoranda; I'm not sure if that was an independent document or not. But I had certainly seen them.

Q. If you look over at the chart on page 5.

A. Uh-huh.

Q. You see projected maximum sales --

A. Yeah.

Q. -- in the right-hand column?

A. Yeah. Those would be Abbott's numbers.

Q. All right. And when you said that the average sales of top five drugs also may be less than 500 million, less than half of Abbott's projected sales, which category of drugs were you talking about, if any particular category?

A. Yeah, I'd have to look at the memorandum again. What page was the statements made on, 2?

Oh, yeah. Right. Okay.

Yeah, I'm talking, I think, mainly about the -- the antibiotic and the cancer markets and it's just the general observation that those are fragmented markets. And specific drugs, particular drugs often have small sales. Not all cancer drugs, not all antibiotics.

Q. But that -- your statement referred to the cancer drugs and the antibiotics?

A. From reading this memorandum just now, this memo, I would say yes.

Q. Then you -- then you -- Number 2, as I read this, you're suggesting that you start with Abbott's sales estimates, but then adjust them downward for market risk factors, correct?

A. Yes, I'm making that general suggestion.

Q. And then you're discussing some of the market risk factors that should be taken into account?

A. Yes.

Q. And those include clinical trial risk factors?

A. Uh-huh, yes.

Q. What are the clinical trial risk factors

that you saw here?

A. Well, again, the cytostatic drugs, just lack of experience with the FDA and -- and fuzzy end points. The -- which one was it, the neuropathic pain -- diabetic neuropathic pain drug and the descriptive memoranda, there was clearly some questions about toxicity, headaches, nausea and things like that. And probably -- I mean, this was so long ago, I can't remember; but looking at it now, I use the same kinds of mental processes, I would say that these are the kinds of things that you have to consider.

Q. Okay. Just -- just picking up on one thing you said a minute ago. You mentioned the neuropathic pain compound, and that's 594, correct?

A. Yes.

Q. And you said that there was some discussions of toxicity, headache, nausea, et cetera?

A. Yes.

Q. Are those all the same thing; is toxicity the same thing as headache and nausea?

A. Depending on how severe, I suppose.

Q. But did you -- when you see toxicity as a

discussion of a risk, is that generally referring to headache and nausea or --

A. No, not -- not generally.

MR. DAVIS: Please, pause for a moment and let him finish his question --

THE WITNESS: Okay.

MR. DAVIS: -- and then pause so that I can object if necessary.

THE WITNESS: Okay.

Q. Generally speaking, toxicity refers to something more serious than headache or nausea, correct?

MR. DAVIS: Objection. You may respond.

THE WITNESS: Yes, generally.

Q. Now, you then say that the market risk factors are -- this is over on page 3, the market risk factors are. And the first bullet is number of competitors. What do you mean by that?

A. Well, the more competitors selling drugs out there, the possibility is less sales for a particular drug.

Q. Second bullet is efficacy and side effects of Abbott's drugs versus competitor's drugs. What did you mean by that?

respect to financial issues?

A. No, I wasn't. But this is very early in the project, and sort of the ground rules weren't established.

Q. Okay. Now, looking further in this document, if you turn to page 7.

A. Uh-huh.

Q. There's a discussion of 594, about two-thirds of the way down the page.

A. Uh-huh. Uh-huh.

Q. This information that you have here, did -- did that come from the descriptive memoranda?

A. Yes.

Q. Okay. Were you interested to know how much higher the dose could be -- could be tolerated than the dosages that are reported here?

A. Yes.

Q. Why was that important?

A. Well, I was worried that the toxicity or the headaches and nausea in this case, not general toxicity, headaches and nausea in this case might be severe enough so that it could hurt the drug's prospects.

Q. So you needed to know -- and -- and how did that relate to the question of whether higher doses could be tolerated? Why was that -- why was that important?

A. It's -- it seemed to me from -- from reading the memorandum and what I've written here is that the dose they're giving people -- so let me read it again.

Phase 2A studies suggested -- okay. I presume I got from the descriptive memoranda that 10 percent of patients at 75 micro -- micrograms by daily had a number of uncomfortable side effects, such as headaches, nausea, et cetera. And they're talking about -- they're talking about Phase 1 studies with 150 micrograms per day, which is just at this level where people are experiencing side effects such as nausea.

Q. So that concerned you?

A. It was a concern, yeah.

Q. And it concerned you why?

A. Excuse me?

Q. Why?

A. Well, because I -- I say there, it might not get -- it might have some risk of not passing

Phase 2 clinical trials; even if it got all the way through, there might be some market risk if a lot of patients couldn't tolerate the drug.
Q. And those -- you got those concerns based on information that Abbott provided you --
A. In the descriptive --
Q. -- in the descriptive memoranda?
A. Excuse me. Yes, in the descriptive memoranda.
Q. And you suggest -- and you say there's some risk of not passing Phase 2 clinical trials, which I think you mentioned a minute ago?
A. Uh-huh.
Q. You then say, "We should perhaps get an assessment from a pain clinical trials expert."
A. Yes.
Q. Did you do that?
A. No, we didn't. No, I didn't.
Q. Why not?
A. I can't speak for Steve.
Well, the project was ended when Steve felt comfortable with everything that he knew.
Q. Well, did you recommend to him that Hancock get an assessment from a pain clinicals

trial -- clinical trial expert?
A. Probably not --
MR. DAVIS: Pause, please. Objection.
You may respond.
Q. You can respond.
A. Beyond this memo, I'm not sure whether I
did.
Q. You -- you said, "We" -- you -- you said,
"We should perhaps get an assessment from a pain
clinical -- clinical trials expert," correct?
A. Uh-huh.
Q. Was there further discussion with
Mr. Blewitt about this?
A. I don't recall.
Q. Do you recall Mr. Blewitt saying, well, we
don't need that?
A. No.
Q. Do you recall following up on this
statement in any way?
A. We followed up in the interview with
Dr. Leonard.
Q. And we'll get to that. But other than
that, did you make any attempt to find a pain --
A. I --

Q. -- clinical trials --

A. I haven't --

Q. You got to let me finish the question.

A. Oh.

Q. Did you make any attempt to find a pain clinical trials expert?

A. We hunted for experts in each field. I haven't reviewed my interview notes prior to this; I would have to look there to give a better answer.

Q. Well, we'll -- we'll take a look at that, but --

A. Okay.

Q. Now, and I have that.

A. Okay.

Q. But assuming there are no notes of any interview with a clinical trials -- trial expert, would it be fair to say that this was not followed up on?

A. Yes.

MR. DAVIS: Objection.

THE WITNESS: Objection? Can I answer?

MR. DAVIS: You may respond.

Q. Yes.

A. It would be fair to say it was not

followed up on except in the Leonard interview.

Q. Why were you concerned that there was a risk of not passing Phase 2 clinical trials based on the data you have?

A. Well, it's right there. The dose that is recommended is around the dose where some patients are experiencing headaches and nausea and a number of other -- whatever the descriptive memoranda said, there were some other side effects listed in there.

Q. That's the 75?

A. Yeah.

Q. Okay. Now, normally speaking for side effects like headaches and nausea, if you increase the dose, is it going to be likely that the side effect was going to be at least the same, but potentially worse?

MR. DAVIS: Objection. You may respond.

THE WITNESS: I -- yeah, I really can't answer that.

Q. Could it be less; could --

MR. DAVIS: Objection.

Q. Could -- could a side effect like headache and nausea at 75 -- is it 75 milligrams; is that

what that is?

A. Yeah.

Q. Could -- could a side effect like headache and nausea be present at 75 milligrams if it's caused by the drug and be less present at 150 or 225 --

MR. DAVIS: Objection.

Q. -- in your judgment?

MR. DAVIS: Objection. You may respond.

THE WITNESS: I mean, it's -- you know, I would say in -- in general, it's likely that side effects would get worse, but I can't speak to a particular -- particular drug.

Q. And when you say, "Phase I studies indicated a maximum tolerated" --

(Interruption for clarification by the reporter.)

Q. You say that, "Phase I studies indicated a maximum tolerated dose of 150 milligrams a day for oral formulation." Do you see that?

A. Micrograms, yes.

Q. Mi -- micrograms.

A. Uh-huh.

Q. Okay. So what did you understand that to

mean, that there was a maximum tolerated dose of 150?

A. I think --

MR. DAVIS: You can respond.

THE WITNESS: Okay. I think the words -- the words there say it. It says maximum tolerated dose, and I presume that comes from the descriptive memoranda.

Q. But as -- as a consultant who's advising Hancock in this area, what did that mean to you? And by that, I mean, what happen -- what would happen if a patient took more than the maximum tolerated dose?

A. Okay. I -- I have to back up. Obviously, I can't answer that question. And in their Phase 1 clinical trials, presumably they were dosing up and I don't know how high. But it -- it -- it waved a red flag as something we ought to talk to Dr. Leonard about and find out what the situation was.

Q. So there was a potential for increased side effects above the 150 micrograms; is that fair?

MR. DAVIS: Objection. You may respond.

THE WITNESS: Yeah, certainly a potential, yes.

Q. And -- and whether or not that was a concern would depend upon the efficacy of a drug at a particular dosing level, correct?

MR. DAVIS: Objection. You may respond.

THE WITNESS: Yeah, there's always a tradeoff between efficacy and side effects, especially in drugs that are badly needed. Or not always a tradeoff, but there can be a tradeoff between efficacy and -- and side effects.

Q. I guess what I'm getting at is you had substantial side effects at a dosage range that was greater than the amount needed for efficacy, but not at the level where efficacy was acceptable, then the side effects would be less of a concern, correct?

MR. DAVIS: Objection. You may respond.

THE WITNESS: Yeah, I -- trying to answer in detail on these things is -- is difficult because basically what it did was raise a red flag.

Q. Right.

A. -- which we were certain we were -- well, not certain. We were going to ask and we did ask Dr. Leonard about.

Q. You asked Dr. Leonard about headaches and nausea?

A. Yes.

Q. Okay. What I'm trying to get at just as a general proposition is in order to evaluate the issue of side effects, in addition to -- in addition to understanding at what dosage level the side effects are occurring and at what frequency, don't you also need to have some understanding as to where efficacy in the drug is achieved?

A. Yes.

Q. Those are related, correct?

A. Yes.

Q. So just for -- by way of crude example and if I -- if I took 20 Vicodin for back pain, I might have pretty substantial side effects that wouldn't be present if I took one.

MR. DAVIS: Objection. You can respond.

THE WITNESS: I can't answer because I don't know about the side effects of Vicodin.

Q. Well, I was just taking any -- any -- any

drug that has some potential side effects --
A. I expect --
MR. DAVIS: Please -- please pause. Let him finish his question, please, and then pause.
Would you please reread the question.
THE REPORTER: "Question: 'Well, taking any drug that has any potential side effects --'"
Q. As a general proposition, my statement is correct, isn't it?
MR. DAVIS: Objection.
THE WITNESS: As a general proposition.
Q. All right. Now, if you could turn to page -- page 8 --
A. Uh-huh.
Q. -- in this document and at the bottom of the page at 2088.
A. Uh-huh.
Q. It discusses ABT-518, correct?
A. (Nodding head up and down).
Q. Is that correct?
A. Yes.
Q. And --

A. That is correct.
Q. -- can we refer to those shorthanded as MMP enzymes?
A. Sure.
Q. Instead of this long word that we're going to -- we're going to butcher, at least I am.
A. Yes.
Q. All right. And -- and the MMP was one of the cytostatic agents that you -- we discussed earlier, correct?
A. (Nodding head up and down).
Q. Is that yes?
A. Yes. Yes.
Q. Now, on page 9, you say, "Abbott states that there are more than 200 compounds in development for cytostatic targets." Is that correct?
A. Yes. This would -- I'm -- I'm relying on what I'm reading here. I don't remember what the descriptive memo said.
Q. Was that a concern to you?
A. Yes.
Q. Why?
A. Market share, competition.

Q. The more competition, the harder it is to get market share?

A. Right.

Q. Then you say in the few paragraphs below that, "These agents have the advantage they can be given in combination with current therapy," et cetera, et cetera. But then you say, "These add-on combination therapies have unusual promise but are high market risk because they are -- are new."

Was that your assessment as of this time, that compounds like 518 were high market risk?

A. At that time, yes; at that time, yes.

MR. WEINBERGER: Okay. I've been told we only have a couple of minutes on the tape. So why don't we take a break.

THE WITNESS: Okay.

THE VIDEOGRAPHER: This marks the end of tape number one in the deposition of Lynn Klotz. Going off the record. The time is 11:07.

(Proceedings interrupted at 11:07 a.m. and reconvened at 11:18 a.m.)

THE VIDEOGRAPHER: This marks the beginning of tape number two in the deposition

BY MR. WEINBERGER:

Q. All right. Mr. Klotz, let us move on.

(Exhibit No. 8, JH 003058 - 003069, marked for identification.)

Q. Dr. Klotz, the -- the cover document on this exhibit, could you identify this as an e-mail that you wrote to Mr. Blewitt on June 27, 2000?

A. Yes.

Q. And are you enclosing in here potential questions for experts with respect to various of the compounds, as well as an introductory statement to them?

A. I'll have to look.

Q. Yeah.

A. Yes, there are questions for experts.

Q. Okay. And the -- the first page of the attachment is a proposed introductory statement to give to the experts?

A. Yes.

Q. And then included in here also are some questions, potential questions for Abbott Laboratories about some of the compounds, correct?

A. Let me look. Yes.

Q. Now, in the -- turning to page -- the page

that has a number on the bottom right-hand, stamped number JH 003060.

A. Uh-huh, yes.

Q. These are questions under the heading Questions for Experts in Cytostatic Therapies.

A. Yes.

Q. In the third paragraph, you say, "One literature reviewed indicated that approximately cytostatic agents for angiogenesis alone are undergoing clinical trials and another 50 agents, preclinical testing. Cytostatic drug development is a crowded field." Was that the conclusion of your literature review to date?

A. I don't remember for sure. It's what I said here.

Q. No reason to doubt that?

A. No reason to doubt it, no.

Q. And then over the top of the next page, you say -- let's say MMPI --

A. Uh-huh.

Q. -- "MM -- MMP inhibitors seems to be an especially competitive area." Is that a correct statement of your views at the time based on the work you'd done?

A. Again, I don't have a direct rec -- rec -- recollection any more, but I wrote it here so I presume it is.

Q. And -- and that's something you wanted to discuss with the experts, correct?

A. Yes.

Q. And it's something you wanted to discuss with Abbott as well?

A. Yes.

Q. Specifically, you -- you wanted to ask Abbott, as it states towards the bottom of the following page, "While Abbott's approaches are clearly cutting edge, how can Abbott achieve a large market share given the large number of competitors in this area"?

A. Where is this?

Q. That would be about here (indicating).

A. On what --

Q. Page 003061.

A. 3061?

Q. Two-thirds of the way down.

A. Two-thirds of the way. Below the -- so read your statement again.

Q. I think I was simply asking, you wanted to

ask Abbott how it could achieve a large market share given the large number of competitors in this area?

A. Yeah.

Q. That was a concern to you?

A. Yes, it was a question to ask, yes, a concern and a question.

Q. Okay. Then there are some selective literature abstracts that are listed in the -- in the end of the document. Did you read all these?

A. Yes, I read them.

MR. WEINBERGER: This would be --

(Exhibit No. 9, JH 003032 - 003057, marked for identification.)

Q. All right. So is the first page of Klotz Exhibit 9 an e-mail you sent to Mr. Blewitt on or about July 3, 2000?

A. Yes, it is.

Q. And -- and these are questions that you had from your research of the cytostatic field, right?

A. Yeah, at this stage, yes.

Q. Now, about four paragraphs from the top --

A. Uh-huh.

Q. -- you state, "The bottom line is that cytostatic therapies is a hot development area, but there are a number of general issues (clinical trial end points, effectiveness, cost effectiveness, competition). Most are not yet in clinical trials, so the probability of a particular compound reaching the marketplace is low. Therefore, cytostatic therapies are more an upside on the investment" -- it says, "in the rest of the basket"; did you mean than the rest of the basket?

A. Likely that's what I meant, yes.

Q. So it was your view as of this time that the likelihood, the probability of any particular cytostatic compound reaching the market was low?

A. Was lower than the others.

Q. Okay. You say here was low?

A. Okay, low.

Q. And you agree with that?

A. Yes. Low is always relative, though.

Q. When you say they're more of an upside, what does that mean?

A. Okay. Often in biotechnology investments, if you're making a presentation of a biotechnology business plan, you have some core areas where you

can calculate market potential, maybe make some reasonable estimates of market share and then you, you know, take into account the probability of success and you go back to net present value. There are some areas where you know that you might have a market, but for one reason or another, it's hard to quantitate. So you just say, well, we're basing our whole investment on this and these other things that may materialize are an upside on those numbers.

Q. So you're basically saying that you -- you should base your investment on the other compounds and then just view this as an upside?

A. That's --

MR. DAVIS: Objection. You may respond.

Q. Is that the thrust of what you were saying?

MR. DAVIS: Objection. You may respond.

THE WITNESS: That's what I was saying at this point, yes.

Q. Okay.

A. I'd like to further answer with one more sentence. Basically, this is just suggestions and ideas for him to consider.

Q. Well, it was reflecting your views based on the work you had done --

A. Yeah, at that point.

Q. -- so far?

And that was about 38 hours' work so far?

A. Yes, at that point, yes.

Q. Just in research on cytostatic, the cytostatic area, right?

A. Yes, these comments were on the cytostatic area, yes.

Q. All right. Now, looking at the -- the document that is attached to this, the -- starts out with potential interviews and questioning. Is this basically another iteration of the document we just looked at with proposed questions for experts?

MR. DAVIS: Objection. You may respond.

Q. And for Abbott?

A. Well --

MR. DAVIS: Same objection. You may respond.

THE WITNESS: Yeah. I mean, I can't remember exactly, but it's later in time so I presume it's been refined somewhat from the previous document.

Q. Okay. Now, over on page 2 of that document --

A. Uh-huh.

Q. -- you discuss -- you have a bullet point that discusses a drug called marimastat; do you see that?

A. Yes.

Q. Was that a drug that was under development by British Biotech?

A. I remember the name but I don't remember much about it.

Q. I think we have some material later that I can show you that -- and I can represent to you that that's a drug that was under development by British Biotech.

MR. DAVIS: Objection. You may respond.

THE WITNESS: Okay.

Q. I'm just telling you.

A. Yeah, he's just telling me. Okay.

Q. So you said, "In one instance, that is in the instance of marimastat, the drug slowed progression but did not prolong life and has painful joint side effects, so there are no life years save" -- I assume that should be saved?

A. Yes.

Q. "And perhaps no quality life years saved."

A. Yes.

Q. So would I be correct to say that you had learned that there were negative results about the -- this potential compound --

MR. DAVIS: Objection.

Q. -- as of July 2000?

MR. DAVIS: You talking about marimastat, this potential compound?

Q. Yeah. Marimastat. If I wasn't clear, right now, I'm talking about marimastat.

A. I would probably call it non-encouraging results.

Q. Where did you get this information from about marimastat?

A. Well, I don't remember any more.

Q. Then in the last paragraph of that section, you say, you talk about the fragmentation of the market, and you say that "sales for an average drug is small, less than 100 to 200 million, yet there are some drugs that do sell over 500 million."

Is it fair to say that you were at this

on page 7. So does this -- was it correct that at this time you were planning to interview Abbott with respect to 518?

A. Again, my memory doesn't inform me, but somewhere in -- along the line in the project I knew we were going to interview Dr. Leonard, and I don't remember if that was the point.

Q. All right. Now, going back to page 6 is again a discussion of marimastat. Do you see that?

A. Yes.

Q. You say, "It has been reported that marimastat has no survival advantage when compared to chemotherapy with gemcitabine. G-E-M-C-I-T-A-B-I-N-E, in advanced pancreatic cancer. With no survival advantage, would the FDA be skeptical about the value of slower progression of the disease since there are serious joint pain side effects (reduction in quality of life)."

Would it be fair to say that you had negative information at this time about the prospects for marimastat?

A. I would say not encouraging information.

Q. All right. If you look over at page 8, I told you I would show you something on British

Q. Okay.

A. They're what page and what document?

Q. The document is ten and talking about the interview with Dennis Carson.

A. Okay.

MR. DAVIS: I object to the question.

THE WITNESS: Now, ask the question again now.

Q. The question is whether any of these questions and answers relate in any way, although it appears to be directed to A-254751, whether they relate in any way to 518?

MR. DAVIS: Objection. You may respond.

THE WITNESS: I think probably not. It's, you know, as you read through, you might find some point in there that could relate to the others, but this was really focused in on A-254751.

Q. Okay. We're done with that one.

(Exhibit No. 11, JH 003014 - 003026, marked for identification.)

Q. All right. Have you had a chance to look at that?

A. Yeah. I just -- yeah, just glanced at the

first page, yes.

Q. All right. So is the first page an e-mail that you sent to Mr. Blewitt on July 11, 2000?

A. Yes.

Q. And that contained the remainder of the research summaries on the proposed compounds, specifically 980, 254751 and 594?

A. The remainder. I'm not sure of. It obviously contains information about those.

Q. Okay. I say remainder because you then say, "I think now you have a complete set of summaries."

A. Well then that would be a fair description.

Q. Then you say, "Let me know, as they are all done." So --

A. All right. You win that point.

Q. You got to take what you can get. All right. Now, you say in the, about two-thirds of the way down, "for A-254751 and ABT-594 there are questions in my mind about whether they will complete clinical trials." Do you see that?

A. Yes.

Q. Let's focus on 594. At this point in

time, what was your understanding of the status of the clinical trial for 594?

A. Now, this is off the top of my head, but I thought it was in Phase II, I believe.

Q. Correct.

A. Yeah, the more I think about it, I knew it was in Phase II.

Q. And you had concern about whether it was going to be able to complete Phase II, correct?

A. Yeah. I was worried about the side effects of nausea and headaches.

Q. And so you said, "That makes it even more important that we see a summary of the latest clinical trial data," right?

A. I said that, yes.

Q. What clinical trial data were you referring to?

A. I am presuming it would be the Phase II data, given that it was in Phase II clinical trials and perhaps Phase I as well. I wrote this comment many years ago, so I can't really say exactly what was in the back of my mind.

Q. Well, do you recall that the clinical studies said the Phase II trial was not going to be

completed until --
A. I don't recall.
Q. Just a minute.
A. Oh, sorry. I thought you were finished.
Q. I'm sorry. It was my fault. I'm making a long pause, but I want to get it right.
A. Okay.
Q. So just be patient with me.
A. Sure.
Q. Let me put it this way: Do you recall that -- being told by Abbott that the Phase II(b), dose ranging trial, again in April 2000?
A. I don't recall.
Q. Do you recall that Abbott told Hancock that a go/no go decision for clinical efficacy was expected in June 2001?
A. I don't recall.
Q. Assuming the Phase II(b) study was ongoing at the time you wrote this, but not complete, what clinical trial data were you referring to when you said we should -- it's important that we see a summary of the latest clinical trial data?
A. I can only answer that question indirectly. And the indirect answer is again I was

worried about the so-called therapeutic index between effective concentrations and side effects. And beyond that, I can't say whether I had particular data in mind.

Q. Did you discuss with Mr. Blewitt going back to Abbott and asking them for any clinical trial data that Hancock didn't already have?

A. I don't recall.

Q. Do you recall in any discussion with Dr. Leonard asking for additional clinical data?

A. Having read that -- reread that interview recently, I don't believe we asked for it.

Q. Even though you concluded that it was even more important that you see a summary of the latest clinical trial data?

MR. DAVIS: Objection. You may respond.

THE WITNESS: Yeah. All I can say is the fact that we didn't ask for it in the interview.

Q. Do you have a recollection as to why you didn't pursue this?

MR. DAVIS: Objection. You can respond.

THE WITNESS: Again, I think about all I can say is at this point Steve Blewitt had

seen a lot of things, things beyond what I was
doing for him, and he was comfortable with
moving forward at this point.

Q. And you don't have any knowledge or recollection of asking Abbott for clinical trial data with respect to 594 and being refused, correct?

A. Yeah. I certainly have no recollection of being refused and am pretty sure that I never asked for any.

Q. All right. Now, attached to this are some potential -- are some Questions For Experts On Neuropathic Pain, correct?

A. Uh-huh.

Q. You talk about a small therapeutic window in the proposed questions; is that right?

A. Yes.

Q. And can you explain what that means, please?

A. The therapeutic window is the difference between the concentration at which a drug is effective and the concentration where there are significant side effects so that you might not administer it, usually expressed as a ratio of one

over the other.

Q. And did you have any particular side effects in mind when you used the words "intolerable side effects" in the definition?

A. Well, I was worried about whether the headaches and nausea would be intolerable.

Q. And that was worry about whether it would be intolerable at the dosage level that was needed for efficacy?

A. Yes.

Q. And is it fair to say that the precise dosage level needed for efficacy was not known at this time?

MR. DAVIS: Objection.

THE WITNESS: I think going back to the descriptive memoranda, that there was information, because I repeat it in other documents, about what the effective dosage was or the kinds of dosages that they were using.

Q. In Phase I?

MR. DAVIS: Objection.

THE WITNESS: I don't know.

Q. I mean, one of the purposes of the Phase II(b) trial is to determine the effective dosage --

that's what it would mean to me.

Q. Now, in the next paragraph you talk about a Merck study and Novartis findings. You seem to be talking about side effects here that appear to be more serious than headache or vomiting; is that fair?

A. Yes, that's what I'm talking about.

Q. And what kind of side effects are you talking about?

A. Well, I'd have to read here.

Q. Okay.

A. Well, I'm quoting from Merck and they talk about hypothermia and life threatening adverse effects, including seizures; so those would be the things I'm talking about from Merck.

And Novartis has other findings, but they don't mean so much to me today because I've forgotten the details.

Q. But they're not about headache and vomiting, are they?

A. No.

Q. Or nausea?

A. No.

Q. They're about more serious --

A. Yes.

Q. -- significant side effects?

A. Yes.

Q. And that's what you refer to when you talk about toxicity and narrow therapeutic window, isn't it?

A. Yes. These are in rats, though, and rats and humans can be --

Q. Oh --

A. -- very different.

Q. -- yeah.

So those were the side effects you were talking about when you were talking about a narrow therapeutic window, right?

MR. DAVIS: Objection.

THE WITNESS: Well, I think when I'm talking about a narrow therapeutic windows in humans, I'm talking more about the observed nausea and headaches that were in the descriptive memoranda and not so much the rat studies. The rat studies are just more of a caution that there could be a problem.

Q. When you raised this with Dr. Leonard, didn't he tell you that they didn't think 594 had

these serious side effects; they just had minor
ones like nausea and vomiting?

A. His comment was something like, and this is from recollection and rereading his interview, that I would take one human over, was it a thousand rats or something like that. I can't remember exactly what his comment was.

Q. Well, can you answer my question which was a little different.

A. Oh, sorry.

Q. Didn't Dr. Leonard tell you that the kind of serious side effects, dangerous side effects that you were raising that had been raised by Merck and Novartis were not present in the upper limit dose, but were only minor, like headache and vomiting?

MR. DAVIS: Objection. You can respond.

THE WITNESS: Okay. He certainly said that the headaches and nausea were only minor and were not serious side effects. My only recollection of what he said about the more serious effects seen in rats was the statement I just made to you.

Now, maybe if I look over the transcript

I've written something else down.

Q. Okay.

A. But my memory was just this comment about he would take one human over a very large number of rats.

Q. But he told you the side effects were minor such as headache and vomiting, correct?

A. Yes, that's what he -- that's what he --

Q. Okay. All right. Let's move on.

(Exhibit No. 12, JH 002999 - 003001, marked for identification.)

(Off-the-record discussion held.)

Q. All right. So can you identify for me the cover page of Klotz Exhibit 12 as an e-mail you wrote to Mr. Blewitt on July 18, 2000?

A. Yes.

Q. And did you attach an interview you had with Mitchell Max about neuropathic pain compounds?

A. Yes.

Q. The neuropathic pain compound in question here was 594, correct?

A. Yes.

Q. And this was the expert that you talked to about 594, right?

A. Yes.

Q. Was there anyone else, any other expert you, either before or after this, talked to about 594?

A. I don't believe so. I believe the other experts were in other areas.

Q. Am I correct that you got all your key questions answered by, is it Dr. Max?

A. Yes. Apparently -- apparently, I did. But whenever I do an interview, it's my standard policy to say I may have a few additional questions at some later time, may I call you back. And if you say that to somebody as opposed to calling them cold a second time, they're generally receptive.

Q. But your feeling as of July 18, 2000 was that you got all your key questions answered?

A. At that point, yes.

Q. So you met all your concerns about -- potential concerns about this compound, you discussed them with Dr. Max?

MR. DAVIS: Objection.

THE WITNESS: I'm going to have to read through to answer that.

Q. Okay.

Q. And that related to some other compound called ABT-924.

A. 924?

Q. Uh-huh.

A. What are we talking about here? We're talking about 524; I think that's a typo.

Q. I was wondering about that.

A. Yes. Yeah.

MR. DAVIS: You mean 594?

THE WITNESS: Yeah, 594. Is there -- I don't even know if there's a 924 in the packet. I think I just had the wrong number in my mind when I wrote the memo would be my guess.

Q. Now, I don't see any specific discussion here about nausea and vomiting. Do you have a recollection that you specifically discussed that with Dr. Max?

A. Well, if it's not in here, I didn't.

Q. Okay.

A. We talked about the therapeutic window and --

Q. Yeah, I see that.

A. -- that's what I was talking about.

Q. Well, the side effects that we looked at before, the significant side effects that Merck and Novartis were talking about --

MR. DAVIS: Objection.

Q. -- that we looked at in the other memo, correct?

MR. DAVIS: Objection.

THE WITNESS: We looked at those side effects. Here I was trying to be as general as possible.

When I stated further back that it would be good to talk to a pain expert, Dr. Max at least appears to qualify as a pain expert. And I was just asking him in general about side effects, about therapeutic windows with side effects.

Q. Okay.

A. So I had in the back of my mind, obviously, the Abbott side effects, but I did not ask the question that way because I was hunting for a general answer.

Q. And he felt the therapeutic window of two was acceptable for pain?

A. That's what he said.

Q. And you accepted that?

A. He's the expert, yes.

Q. And you were satisfied with that?

MR. DAVIS: Objection.

THE WITNESS: Well, satisfied, satisfied is too strong a word. It just says that in this kind of pain therapy, chronic pain therapy, as in cancer therapy, you can accept therapeutic windows which are not -- far from ideal because the problem is a severe problem. Cancer is deadly. Neuropathic pain as I understand it is very difficult to deal with for people. So it's -- I wouldn't say I would accept it as an acceptable answer; I accepted it as a fact of the field.

Q. Well, you accepted it in the sense that you didn't go seeking any additional experts to develop the point further?

A. Let me look at the date on this. July 18. We're very close to the interview with Leonard, and then after the interview with Leonard, the project ended. So --

Q. Right. But your recollection is you did not consult any other expert --

A. Well, no, I did not consult any other experts, no.
Q. -- on neuropathic pain?
A. No. To my recollection, yeah.
(Exhibit No. 13, JH 002984 - 002988, marked for identification.)
Q. Before we look at that document, I wanted to ask you one other thing about the last exhibit.
A. Uh-huh.
Q. You say in the e-mail, this is Exhibit 12, "The bottom line is that all drugs for neuropathic pain are mediocre." What did you mean by that?
A. Well, that's what Dr. Max said. He said they're all mediocre.
Q. What did you understand that to mean?
A. They don't work so well, they have side effects or some combination of those two.
Q. Just kind of goes with the territory; is that what he was saying?
MR. DAVIS: Objection.
Q. I'll strike that.
A. At that time in that territory --
MR. DAVIS: Objection. He's -- he's withdrawn the question.

THE WITNESS: Okay. Fine. I missed that part.

Q. What he was saying was at that time -- to your understanding at that time that the drugs available for neuropathic pain either didn't work so great or had side effects or both?

MR. DAVIS: Objection.

Q. Is that fair?

MR. DAVIS: Objection. You can respond.

THE WITNESS: I can respond? Okay. Or some combination of those two.

Q. Or some combination.

A. Yes.

Q. All right. Now, looking at Exhibit 13, is the cover document an e-mail you wrote to Mr. Blewitt on July 23?

A. Yes.

Q. Working Sundays, I see.

A. Yes.

Q. And was this a list of -- a continued refinement of a list of questions that you wanted to ask Abbott?

A. Yes.

Q. Now, on the second paragraph on the page

that's stamped 002986 --
A. Uh-huh.
Q. -- you say, "From your descriptive memorandum, ABT-594 appears to have a therapeutic window of only two to three."
Is it your recollection Abbott disclosed this therapeutic window in the descriptive memorandum?
A. I think it was my interpretation of reading the material in the descriptive memorandum.
Q. The information necessary for you to get to that conclusion was disclosed in the memorandum, correct?
MR. DAVIS: Objection. You can respond.
THE WITNESS: I think so. I'd have to go back and look at the memorandum.
Q. We'll do that. I'm not trying to hide it from you. We'll get there.
A. No.
Q. All right. Over on page 2988, the last page --
A. Uh-huh.
Q. -- you're talking about cytostatic drugs and you say, "In this regard" -- and this is I

guess a proposed discussion with Abbott -- "In this regard metalloproteinase inhibitors are particularly worrisome."

Am I correct that 518 was a metalloproteinase inhibitor?

A. Metalloproteinase inhibitor, yes.

Q. And that was particularly worrisome to you based upon what you had learned, correct?

A. Uh-huh.

Q. Is that yes?

A. Yes. Excuse me.

Q. And you also repeat here what we talked about earlier with respect to the findings on marimastat. Do you see that?

A. Yes.

Q. Then you say, "Abbott states that marimastat has dose limiting joint side effects."

Is that your recollection that Abbott had told you that marimastat had these problems?

A. Well, until the Leonard interview, I never talked directly with Abbott, so I'm presuming that was in the -- the --

Q. The memorandum?

A. -- the memorandum, yes, descriptive

memorandum.

Q. You recall that you did ask Abbott about marimastat, correct?

A. I recall I asked Abbott those questions in the context of 518. I don't recall offhand whether I had mentioned marimastat.

Q. Do you remember specifically Dr. Leonard talking about British Biotech and marimastat?

A. No, I don't remember.

MR. WEINBERGER: This would be a good time to break for lunch if you want.

THE VIDEOGRAPHER: Going off the record. The time is 12:14.

(Proceedings interrupted at 12:14 p.m. and reconvened at 1:17 p.m.)

(Exhibit No. 14, e-mail dated July 11, 2000, marked for identification.)

THE VIDEOGRAPHER: Back on the record. The time is 1:17.

BY MR. WEINBERGER:

Q. Good afternoon, Dr. Klotz.

A. Good afternoon.

Q. You have in front of you Klotz Exhibit 14. It's an e-mail dated -- can you just verify for me

that the cover sheet is an e-mail dated July 11, 2000 from you to Mr. Blewitt?

A. Yes, it is.

Q. And is this enclosing additional information on the neuropathic pain situation?

A. Yes, it is.

Q. So this is an update of the document we looked at before?

A. Yes.

Q. All right. I just wanted to get that into the record. We don't need to go into it.

Let me get the next document for you.

(Exhibit No. 15, JH002973 - 002979, marked for identification.)

Q. Is the attachment to the e-mail the notes of the Leonard telephone interview that you discussed earlier in your testimony?

A. Yes.

Q. Was there a later version or as far as you know is this the one?

A. No. This was the last version.

Q. Okay. And when -- can you tell me when you had this telephone interview with Dr. Leonard?

A. I don't remember exactly. I'm surprised

it's not on the memo.

Q. But it was sometime before July 28, 2000?

A. Yes.

Q. Then after the telephone conference, you wrote up these notes to reflect your best recollection of what transpired; is that correct?

A. Yes.

Q. And am I correct that you concluded that there was no indication of any deception on Abbott's part after this interview with Dr. Leonard and the other people from Abbott?

A. Yes.

Q. And am I correct that except for one question regarding the patent issue on 594, your questions were answered satisfactorily?

A. I have to qualify that answer, because I can't remember what the -- what the issue was with the patent on 594; but I would say that my questions otherwise were answered satisfactorily.

Q. Okay. Okay. You also say in the e-mail, "Let's talk to see where we go from here and to discuss the format of the final report."

Was there a final report that you were expecting to produce for Hancock at this stage?

MR. DAVIS: Objection. You can respond.
THE WITNESS: Uh-huh. I think I was asking what he really wanted to do next.
Q. When you say "to discuss the format of the final report," had you previously talked to him about producing a final report as part of your work?
A. I can't remember.
Q. Did you ever produce a final report?
A. No. This was it.
Q. So after this write-up of the Leonard interview, you produced no further work product in connection with your engagement; is that correct?
A. No further work product is correct.
Q. And you did no further work; is that correct?
A. No further work.
Q. Did Mr. Blewitt tell you not to do anything further?
A. He did not tell me directly or even indirectly.
Q. He just didn't ask you to do anything else?
A. He just did not ask me to do anything

recollection again was that this was before Abbott, not after Abbott.

Q. So you have a clear --

A. But I could be --

Q. -- recollection that after your interview with Dr. Leonard you did no further work?

A. Yes, that is a clear recollection.

MR. DAVIS: Please let him finish the questions, then pause.

THE WITNESS: I thought he had finished.

Q. So were you aware that there was a change in one of the compounds; an additional compound -- one compound was discontinued and another was added to the basket af --

THE WITNESS: No, I wasn't.

MR. DAVIS: Let him finish the question.

THE WITNESS: Sorry.

Q. -- after July of 2000?

MR. DAVIS: Objection. You may respond.

THE WITNESS: No. I was not aware until I recontacted four or five years later --

Q. Okay. So in other words are you --

(Interruption by the reporter.)

THE WITNESS: Later with Choate Hall and

Stewart.
Q. Okay. So it's quite clear that in your mind that Mr. Blewitt never contacted you to ask you to do any further evaluation on additional compounds after your interview with Dr. Leonard?
A. It's clear in my mind, yes.
Q. Okay. All right. Let's look at the -- let's look at the interview memo.
A. Uh-huh.
Q. What number is that, sir? 15?
A. 15, I think, yeah.
Q. Were there three people on this call from Abbott?
A. Yes.
Q. Now one was Dr. Leonard. One was -- was the second one Phil Demer (phonetic).
A. I got his name just the other day, but I didn't know it until then.
Q. And the third was Steve Cohen?
A. Yes.
Q. And you were on the call with Mr. Blewitt?
A. Yes.
Q. Were you in the same room as Mr. Blewitt?
A. No. We called from, I believe from

Hancock's offices.

Q. So were you and Mr. Blewitt together?

A. We were together -- oh, that's a good question. Were we together? I don't remember.

Q. Did you take notes of this interview?

A. Yes.

Q. Handwritten notes?

A. Handwritten notes.

Q. What did you do with them?

A. When everything from that project got destroyed, I presume they got destroyed with them.

Q. Do you know if Mr. Blewitt was taking notes?

A. I can't remember.

Q. Let's look at the notes on 594.

A. Uh-huh.

Q. The statements in italic, were those questions that you asked Dr. Leonard?

A. Yes.

Q. Did you ask the questions or did Mr. Blewitt ask the questions?

A. I asked the questions.

Q. And was -- is the written description of this question that starts from your descriptive

memorandum "594 appears to have a therapeutic window of only two to three," et cetera, is this an accurate description of what you asked him?

A. I think I probably read the questions directly.

Q. Okay.

A. I can't say certainly, it's been so long, but I think I probably did.

Q. Now, are the answers that are here as close to verbatim as you could get them?

A. As close to verbatim as I could get them from handwritten notes, transcribing them within a few days after the interview; that was usually my style. I can't say the exact time period between the two there.

Q. And you meant to include every point you thought was important, correct?

A. I meant to include points, tried to capture the way things were said as well as possible from the handwritten notes.

Q. Now, with respect to 594, in response to your question about therapeutic window, you state Dr. Leonard said, quote, when we give patients the upper limit dose, the side effects aren't

dangerous, colon, headache, comma, vomiting.

A. Now where is this exactly?

Q. That's at the bottom of page 2975.

A. Okay.

Q. Is that what he said to you?

A. Yeah. I would say to the extent that I had to paraphrase, that's was what he said, yes.

Q. So he told you that patients who were given the upper limit dose experienced headache and vomiting, correct?

MR. DAVIS: Objection. You can respond.

THE WITNESS: Yes, he did.

Q. And he categorized those as minor side effects?

A. Yes, he did.

Q. Did you ask him any further questions about headache and vomiting?

A. I can't remember.

Q. Is there any reason if you had asked further questions or had further concerns you wouldn't have put them in this memo?

A. Again, I can't remember exactly, but I think they would have been in the memo.

Q. Is there anything else that you believe

Mr. -- Dr. Leonard said about this that you didn't write down?

A. Not that I remember.

Q. What did you understand him to mean when he said the upper limit dose?

A. I would -- at the time, I can't say what I thought. I can answer looking at it now.

Q. What do you think it means looking at it now?

A. I think maximum dose that they used in the clinical trials in Phase II.

Q. Well, he didn't have the results of the clinical trials in Phase II at the time of this call, did he?

MR. DAVIS: Objection. You can respond.

THE WITNESS: Well, he seemed to know what concentrations were being used; they were in the descriptive memorandum.

Q. Right. But the results of this trial were not -- you didn't understand that the results of this trial were available --

A. Well --

MR. DAVIS: Please let him finish the question and let me object. If necessary.

Q. He was telling you the opposite, right?

MR. DAVIS: Objection. You can respond.

Q. I'll strike the question.

A. That makes more sense.

Q. It's just an argument.

A. Okay.

Q. It's just rhetorical.

A. Okay.

Q. So sitting here today you don't know what dose limit he was referring to when he talked about the upper limit dose?

A. No.

Q. Do you remember we looked at a document earlier that talked about 150 micrograms as being an upper limit dose?

A. Yes. I remember the document.

Q. Do you think he might have been referring to that?

MR. DAVIS: Objection.

THE WITNESS: Again, I'd have to speculate.

Q. Okay. Looking at the entire discussion on 594, is there anything that you recall Dr. Leonard saying that you have not captured in this interview

memo?

A. Again, I can't recall.

Q. Well, I'll ask the question, is there anything you can recall Dr. Leonard saying that is not in the interview memo?

A. Yes. I can't recall that either.

Q. So just to be clear, there's nothing you can recall Dr. Leonard said on the 594 that's not in this document, correct?

A. Not at this point in time many years later, I cannot recall, yes.

Q. Okay. Now, looking over at page 2977 -- strike that.

Go back to 594. I take it you didn't ask him for any clinical trial data, correct?

A. No. I did not. I took him at his word.

Q. Well, and Dr. -- I'm sorry -- Mr. Blewitt didn't ask him for it either, correct?

MR. DAVIS: Objection.

Q. On this call.

A. I don't recall that he did or not.

Q. Now, you did ask him for some pharmacokinetic data with respect to another compound, correct?

A. No, I understand. Yeah.

Q. All right. Then there's a discussion of cytostatic drugs, except for ABT-627. Am I correct that that discussion would have included the 518?

A. I presume, yes, it would have included.

Q. And along the lines of the questions that you had formulated earlier that we talked about, you asked him about the -- strike that.

You told him your view that this was a crowded field with a lot of competitive products, right?

A. Uh-huh.

Q. Is that yes?

A. Excuse me.

MR. DAVIS: Objection. You can respond.

THE WITNESS: Yeah. I'm just trying to see where I said that in here. Oh, top question; okay. Yes. In the top question, I did.

Q. And his reply was, "I agree that for cytostatic drugs in general there may be 50 to 200 in testing. To get the market lead, get one that works. In this business there are a number of people who start things, many more than the ones

who finish."

Is that basically what he said?

A. Yes, that's basically what he said and I would say that's a fair answer.

Q. Why is it a fair answer?

A. Well, a lot of companies, biotech companies, and I suppose even pharmaceutical companies as well, have ambitions, and for some reason things drop out long before they get anywhere near market.

Q. It happens to pharmaceutical companies, too, doesn't it?

A. Yes, it does.

Q. Including companies like Abbott?

A. Yes. Pharma has some statistics, I can't remember the exact numbers, but the numbers of the drugs in discovery that actually end up going into clinical trials; there's a huge, huge difference between the two.

Q. Yeah. There's many, many more drugs that go into discovery in clinical trials than ultimately are marketed?

A. Yes. And even things that enter clinical trials still today only 20 percent make it out the

other end. So yes.

Q. Do you have any understanding for the reasons for those statistics?

A. Yeah, I do. And I can give you a lecture on it actually.

Q. Well, not a lecture, actually --

A. I'll do it in a couple of minutes.

Q. Always the teacher.

A. First I start noting that the success rate for drugs out of clinical trials 20 years ago was 20 percent, and today it's not much different. In fact, if anything it may be slightly less. But let's say it's 20 percent.

And then you have all of modern biotechnology, which is certainly guiding the development of most drugs these days, except for sort of follow on drugs from existing drugs.

And so it's a legitimate question. We have all this biotechnology. We have the Human Genome Project which is identifying targets. Why don't we have a better success rate in clinical trials? And plus, there are a number of companies out there that are looking specifically at improving the success rate of clinical trials.

MR. DAVIS: I don't think that actually
describes what he was consulted on --

THE WITNESS: No, it --

MR. DAVIS: -- but you can respond.

THE WITNESS: -- doesn't describe because
that's putting numbers on things and that was
not my job in this particular project.

Q. Well, you weren't quantifying but --

A. I was not quantifying.

Q. -- you were trying to evaluate the
likelihood that these compounds would be successful
and would be successful both from a scientific
point of view and from a competitive point of view;
is that fair?

MR. DAVIS: Objection. You can respond.

THE WITNESS: Qualitatively, yes.

Q. So with that in mind is why I'm asking you
for your view as to why the success rate for new
drugs has been so low historically.

A. That's too --

MR. DAVIS: Objection. Objection. I
don't think that follows, but you can respond.

THE WITNESS: That's too -- that's too
general a question because the success rate

depends on the particular drug and the particular type of drug and things like that.

I mean, I could tell you where they fall out of clinical trials; something like 25 percent fall out in the safety trials. And that reflects the fact that mice studies, although they're necessary to get something into clinical trials, are -- mice are very different than humans and other animals as well.

I think it's another -- again, these numbers are off the top of my head. I mean, I have them written down in type -- other places. Something like 40 percent fail in Phase II. And three reasons: One of which is they turn out not to be efficacious enough or efficacious in humans. Second reason is that safety trials, although not formal, safety is still being monitored all the way through, and some fall out for safety reasons. And I don't remember the percentage off the top of my head.

Others fall out for business reasons. The company may just decide it's not going in that

direction. It can make any number of business decisions for dropping something out of clinical trials.

Once things are through Phase II the probability is fairly high that they will get through Phase III. And again, I can't remember the number. Maybe at that point, 70 to 80 percent, something like that.

And if they successfully completed Phase III and have an NDA, the probability is still not 100 percent that they get marketed because there could be a business decision or some sort of late, you know, late effects, side effects showing up or something like that.

So those are the general reasons, but it really is very much class of drug dependent.

Q. Well, why would a company drop a compound for business reasons that had not failed clinical trials? I think you indicated that that happens.

MR. DAVIS: Objection.

Q. Why would that happen?

MR. DAVIS: Objection.

THE WITNESS: Should I answer that?

MR. DAVIS: To the extent that you know

and don't speculate.

THE WITNESS: It's pure speculation as to why a company might drop a particular drug.

Q. I understand you couldn't speculate on why a particular company dropped a particular drug. But in general, could you give me kind of the range of reasons why that might happen if you have an understanding of that?

A. Yeah. A competitor gets a drug in the marketplace and it looks pretty good, and it doesn't look like the particular drug that his company has is going to measure up to the competitors'.

Pharmaceutical companies change at least sub-strategies if not major strategies from time to time. And they may just decide they're going to go in this direction and not that direction. And there could be, you know, anticipated technical issues, anticipated regulatory issues, I mean, there's any host of reasons, but it's all speculation in a way. So --

Q. Okay. Now in response to your question, which is on 2978, concerning the number of agents in clinical trials and in preclinical testing.

Other than what you wrote down here, did Mr.
Leonard say anything else about this in response to
this question that you can recall?
A. Again, I really can't recall the details.
I certainly tried to get everything that was
important down.
Q. Okay. That's fair enough.
All right. If you look over to page 2979,
did you tell Dr. Leonard that metalloproteinase
inhibitors -- I'm sure I'm mispronouncing that.
A. Metalloproteinase.
Q. Inhibitors are particularly worrisome?
A. Uh-huh.
Q. And you told him that -- you discussed
with him the literature findings about marimastat
having no survival advantage in advance pancreatic
cancer?
A. My best recollection is I read these
questions verbatim, so I would have.
Q. Okay. And you also said, "Could failure
for approval of marimastat make the approval
barriers higher for follow on drugs?"
Was it your information at that point that
marimastat would likely fail the approval -- fail

to get approval?

A. I think from reading this question here -- again, my memory doesn't inform me on this -- that I'm just asking, you know, an if, what if question, could failure for approval of marimastat make the approval barrier higher for follow on --

Q. Well, you understood based on the information you had about marimastat that it might not be approved?

A. I was -- I was, either based on information or my general knowledge of clinical trials and my general concerns about cytostatic drugs might have been enough for me to word that question in that way.

Q. Dr. Leonard didn't tell you that he thought marimastat would be approved, did he?

A. No, I don't think he did.

Q. In fact, he said that it was -- British Biotech had problems with marimastat, correct?

A. Yes.

MR. DAVIS: Objection. You can respond.

A. Yes, that's what he's saying, yeah.

Q. In fact, he said that marimastat was not selective enough, right?

A. Yes.
Q. And he said that Abbott's drug had an enzyme that would avoid the kind of joint side effects that marimastat apparently had?
A. That's what he's saying there implicitly, yes.
Q. And you never got any information that that was incorrect, did you?
A. No.
Q. Is there anything about the 518 that Dr. Leonard said in this interview that is not recorded in this memo?
A. Not that I remember; but I don't remember is probably the appropriate answer.
Q. Okay. And I know -- I think I've asked you this before, but just to make sure: Is there anything else that came up about anything in this interview that is not recorded in these notes?
A. I don't remember. Again, I tried to get everything important down that I was able to catch in my written notes.
Q. Okay. Now, when you wrote in the cover e-mail, "there's certainly no indication of any deception on Abbott's part," why did you write

that; was someone concerned about deception on Abbott's part?

A. I think we were concerned about -- or not concerned about -- but the project goal. The goal as we saw it was to make sure that what we read in the descriptive memoranda, which described all these drugs fairly completely, was consistent with what we could find out on the outside. If we found something that was really inconsistent, one might characterize it as deception, but that did not necessarily have to be the word that I used there; I could have used inconsistency.

Q. Mr. Blewitt hadn't suggested to you that he thought Abbott was deceiving him in some way?

A. No.

Q. That didn't come up?

A. No. The working assumption was that Abbott was accurate in what they said. But we felt we had to verify it, make sure what they said was consistent with what we found on the outside.

Q. Okay. And that was your conclusion that --

A. Yeah.

Q. -- what you found on the outside was

consistent with what Abbott said?

A. And Leonard's interview, yes.

Q. All right.

(Exhibit No. 17, JH 001203 - 001220, marked for identification.)

Q. Aside from the consulting work that you are doing with Choate, have you ever seen this document before?

A. No, besides the consulting work. In fact --

Q. Did you see any -- go ahead.

A. In fact, I think I saw it for the first time either two days ago or this morning.

Q. All right. Did you -- did you ever see any drafts of this document?

A. No.

Q. Did Mr. Blewitt ever discuss with you a recommendation memo that he was preparing for the investment internally in John Hancock?

A. No.

Q. Over on page 1209 the document has a summary of estimated sales. Would you take a look at that.

A. Uh-huh.

own calculations when I do these kinds of things.

Q. You didn't discuss the Lehman curve --

A. No.

Q. -- with Mr. Blewitt?

A. No. I discussed my own in some memo way back.

Q. All right. Over on page 11, which is stamped 1213 --

A. Okay.

Q. -- the document discusses the due diligence process. You see in the middle of the indented paragraph it says, "We engaged Dr. Lynn Klotz to search the major drug and medical databases," et cetera, et cetera.

A. Uh-huh.

Q. Can you read from there to the end of the paragraph and tell me if there's anything in there that you disagree with?

A. "We engaged Dr. Lynn Klotz" --

Q. You can read it to yourself.

A. Okay. Yeah, I don't see anything I disagree with in there.

Q. And his conclusion, in summary, none of our diligence revealed any information that was

materially different than what Abbott had provided
to us. End quote. You'll agree with that,
correct?
A. I agree with it, yes, at the time I
completed the project, yes.
Q. Have you ever used Monte Carlo simulation
to model returns on a portfolio of drugs?
A. I've used Monte Carlo simulations, but not
for returns of portfolios of drugs.
Q. What were you --
A. For scientific endeavors.
Q. Not for scientific endeavors.
A. No, for scientific endeavors.
Q. For scientific --
A. For scientific.
Q. But not in connection --
A. Not in connection with --
MR. DAVIS: Please, let him finish his
question.
Q. All right. Have you ever used the DiMasi
study to determine the probability of success of
various drugs?
A. Yes. I've used his, and I've used a few
others which I couldn't recite to you right now. I

think my approach was to average the various studies. They weren't all that different, so --

Q. And DiMasi study, could you describe what that is?

A. Well, he was evaluating the average cost of taking a drug from discovery to the marketplace, and he looked at, I can't remember the exact number, but something like 100 drugs out of pharmaceutical companies.

He had three versions of that study. And the two I'm familiar with was the one in the mid-90s, and then he repeated it, oh, I don't know, 2003 maybe, something like that.

And he found that with the appropriate discounting of money and all those things and taking into account that drugs that made it to the marketplace also had to reflect the cost of drugs that failed, he found it cost over $800 million to take an average drug through discovery, clinical trials, and on to the marketplace.

Q. That's with respect to the cost. What I'm interested in is the probability of success.

Have you used any of his calculations to determine or estimate the probability of success of

Q. -- with respect to that model --

A. Yes.

Q. -- right?

But he did not ask you to use that model or to help him in any analysis in this transaction, correct?

A. He did not ask me, no.

Q. Okay. I appreciate you waiting.

Let's just for the purpose of completeness mark the document which I think is the one you're referring to.

(Exhibit No. 18, JH 000695 - 000727, marked for identification.)

Q. There's no date on the cover of this report. Do you think this was sent at the end of your work?

A. No. I think -- well, I don't know for sure; likely in the middle somewhere.

Q. And what prompted you to send this material to Mr. Blewitt?

A. Well, I was not involved in the financial end. And I just didn't have any measure of the degree of expertise that they had in pharmaceutical calculations. So I just wanted to make sure that

he was aware of this.

Q. I'm sorry. You say you did have expertise in the subject?

A. I have expertise, yeah. I wasn't sure what the level of expertise at Hancock was because I was not involved in the financial stuff.

Q. This represents a model that you've used in your work to predict expected internal rate of return for investments in drug development?

A. And sometimes MPV.

Q. Sometimes MPV. And after you sent this to Mr. Blewitt, did you have any further discussions with him about this?

A. He said that they had the -- these are my paraphrase, I can't remember his exact words. He said that they had the financial end taken care of or were taking care of it or something like that. He indicated that they had all that under control. Again, my own words, not his, because I can't remember what his words were, but I remember the gist of them.

Q. All right. Let's go back to -- I want to ask you about this formula here on page 8, but I think I'm going to pass it up.

MR. DAVIS: Be my guest.

THE WITNESS: My excuse is I'm a mathematician. I don't like to sort of model things if I can get an analytic solution, so I want to get an analytic solution.

Q. I'd ask you about it but I don't want to show off.

A. It's geometric series and probably derivatives of geometric series. You don't want to ask.

Q. Back to Exhibit 17.

A. 17; okay.

Q. This is page 13, which is stamped 001215.

A. Yeah.

Q. And you see a box that has the list of compounds?

A. Uh-huh.

Q. And in phase, and then JH probability of approval. Do you see that?

A. Uh-huh.

Q. Do you have any information as to where these probabilities came from?

A. No, I don't. I can tell you they didn't get them from me.

Q. They did not get them from you?

A. Yeah. Because my probabilities at that point were not broken down into different product categories.

Q. Meaning you had only one number or groups of numbers?

A. Yeah, for Phase III, I had one number and, you know, average over things, and Phase II, I had one number.

Q. What were your numbers?

A. Say it a slightly different way. 20 -- the numbers I just gave you before, something like 20 percent from beginning to end. And they weren't -- they weren't cast as -- well, they were cast as probability of approval, I guess. And you increase things something like 40 percent when you get through Phase II. I can't remember the exact numbers, but I've got them. And --

Q. Did you provide such numbers to Mr. Blewitt in writing?

A. If they're not in that memo where I'm describing my evaluation methodology, then I did not provide them.

Q. In the one we just marked?

A. Yeah. My recollection is that's the only time I brought that up. And when he said that they had the financial stuff, again, my paraphrasing, under control, that they were, you know --

Q. Can you look through there to see if there's anything that would represent that kind of estimate?

A. In that -- in which --

Q. In Exhibit 18, I think it is.

A. 18? Yeah, I can do that.

Yeah. On page 3 of the second document that's in there. JH 000702.

Q. Got it, yeah.

A. Yeah.

Q. So if I understand this correctly, you were assigning a .115 probability of a drug in preclinical reaching the market?

A. That -- that really depends on where it is in preclinical. That just happens to be in the example that I used here. It could be much lower, something early in preclinical, problematic drug, it could be lower; and that's one that's hard for anybody to estimate when it's in preclinical.

Q. And why -- and it's 23 percent chance of

drug in Phase I?

A. Uh-huh.

Q. And 30 percent chance of a drug in Phase II?

A. Yeah.

Q. And these are accumulative. In other words, the 30 percent takes into account the percentages in the previous case?

A. Yes.

MR. DAVIS: Objection.

THE WITNESS: It's from there to the end.

MR. DAVIS: When you say 30 percent, what are you referring to?

MR. WEINBERGER: The Phase II, point 306.

MR. DAVIS: Point 306; okay.

Q. That's 30.6 percent, right?

A. Yeah.

I can tell you today I use a higher probability for Phase II.

Q. Today than in 2000?

A. Than in 2000.

Probably based on more recent data. I mean, this model just gets dusted off once every few years, so my memory isn't exactly sharp on it.

Basically, this was just an illustration for him of what I would do. It doesn't use any real data that would relate to Abbott in any way.

Q. Is there anything in here that would relate to -- well, strike that.

The numbers in this chart on page 3, I understand they don't relate to Abbott, but is this based on some kind of industry wide information?

A. Yeah, I think --

MR. DAVIS: Objection. You may respond.

THE WITNESS: At the time I had DiMasi's numbers, and there's a fellow Ashley Stephens, who at that time was head of licensing at Dana Farber.

Ashley has a degree in chemical physics from Oxford. The reason I know all this is he was -- he was a -- he was vice-president of marketing. He got appointed -- he got promoted to that position at some time during my stay at BioTechnica. And I have a physical chemistry background, so we could talk back and forth about mathy things.

Independent of me, he developed a model to do the same thing. And he published a paper

on it. I can't remember where it was
published now.
He gave a lecture in my course on the
model, but we noted that we had both done this
independently because as mathematician types,
we think alike.
And these numbers I think are probably the
average of all his plus DiMasi's. I can't
remember exactly what they are at this point.
Q. Okay.
A. But it's more than one that went --
Q. Okay.
A. -- into that average at that point.
Q. Okay. Got it.
MR. WEINBERGER: The reporter tells me
we're about out of tape so maybe we'll take
our break now.
THE WITNESS: Okay.
THE VIDEOGRAPHER: The marks the end of
tape number two in the deposition of Lynn
Klotz. Going off the record. The time is
2:14.
(Proceedings interrupted at 2:14 p.m. and
reconvened at 2:28 p.m.)

THE VIDEOGRAPHER: Back on the record.
Here marks the beginning of tape number three in the deposition of Lynn Klotz. The time is 2:28.

BY MR. WEINBERGER:

Q. Dr. Klotz, could you look at -- we were looking at Exhibit 17 before.

A. Okay.

Q. I want to continue to ask you a few questions about that.

A. Uh-huh.

Q. Page 13, which is stamped 001215, please.

A. Uh-huh.

Q. Forgive me if I asked you this. Everything is kind of melding together.

But did you have any input into the probability of approval percentages that are listed on this?

A. No input.

Q. If you'd look at the page beginning at page 16, 001218.

A. Uh-huh.

Q. And there's a description of compounds. Did you prepare any of these descriptions?

A. No.

Q. Okay. Page 17 under the heading 594, in the third paragraph, the document states, quote, our scientific consultant, Dr. Mitchell Max, NIH, eliminated an initial concern of ours that the, quote, therapeutic window, end quote, of ABT-594 was too short and would potentially block approval. Dr. Max indicated that ABT-594's therapeutic window was acceptable.

Does that accord your recollection?

A. Yeah. I think my interview notes say pretty much the same thing in other words.

Q. So you knew what the therapeutic window was, and the question was whether that was going to be acceptable for this kind of a compound, right?

MR. DAVIS: Objection. You can respond.

THE WITNESS: I was estimating what the therapeutic window was. But the red flag over possible side effects of 594 did not disappear until I talked to Dr. Leonard. And at that time he said it was not a serious issue, and so at that time I didn't see a problem.

Q. Which side effects are you talking about?

A. Well, headache and nausea were the two.

THE WITNESS: I can't, you know, it's hard for me to answer that. You're asking me to speculate what --

Q. Well, do you think vomiting is a dangerous side effect?

A. Could be.

Q. And if Mr. -- Dr. Leonard told you that vomiting wasn't a dangerous side effect, you might still believe it was a dangerous --

A. Was the word dangerous in my -- is that a word you chose or is that in my --

Q. It's in your notes.

A. Okay. As opposed to serious.

MR. DAVIS: Objection.

Q. Yes.

He says, "When we give patients the upper limit dose, the side effects aren't dangerous, headache, vomiting"; that's what your notes say.

A. That's what I said?

Q. That's what your notes say he said.

A. Oh, well --

MR. DANIEL: Objection, in part. You may respond.

THE WITNESS: Okay. Yeah. If he said it,

that's -- it probably was -- again,
remembering back to 2000, I don't have a
memory of anything -- I don't have a memory of
exactly his words. I'm presuming those were
his words, which is why they ended up in --
but it's a presumption.

Q. Now, this description here on page 17 doesn't say anything about nausea and headaches and vomiting, does it?

A. It implicitly does when it talks about the small therapeutic window.

Q. That's what Dr. Max said was acceptable?

A. For these kinds of drugs he said it was acceptable.

Q. Dr. Max said that?

A. Dr. Max said that.

Q. Dr. Max is not an employee of Abbott?

A. No, not that I know of.

Q. He's the person that you went to for an independent --

A. Yes.

Q. -- opinion?

A. Yeah.

Q. All right. Now, over on page 18.

A. Uh-huh.

Q. Strike that. Strike that.

All right.

(Exhibit No. 19, JH 008153 - 008209, marked for identification.)

Q. Do you recognize this document?

A. This looks like one of Abbott's descriptive memorandum. It says it on the front cover, yes.

Q. Actually, I think they're all in there.

A. They're all in there; okay.

Yes, I recognize it.

Q. I think you testified earlier you got Abbott's descriptive memorandum before you started your work or when you just started your work?

A. At the beginning, yes.

Q. So you had the ability to read these and ask any questions you wanted that arose out of them, correct?

MR. DAVIS: Objection. I'm going to note, these ones are dated February '01.

MR. WEINBERGER: Well, these are the ones that were ultimately filed; but for the most part they're the same.

THE WITNESS: Well, I never saw the February 2000.

Q. I don't have anything from your files so I can't pin down what you did have and what you didn't have.

MR. DAVIS: You're asking him whether he saw these. And my point is these are dated from February of '01. There were a variety of versions of the descriptive memorandum.

THE WITNESS: I have never saw these.

Q. Well, to the extent that they're the same, you saw them.

MR. DAVIS: Objection. You can respond.

THE WITNESS: To the extent they're the same, I saw them, but I don't know to what extent they're the same.

Q. We can look at that.

But you did get descriptive memoranda that look like these in format in --

A. In the --

Q. -- with respect to each of those compounds?

(Interruption by the reporter.)

Q. -- that look like these in form for each

of the Abbott compounds that you were evaluating
before you started your substantive work.

MR. DAVIS: Objection. You may respond.

THE WITNESS: Yeah. I -- I would have
trouble answering that question, too, because
it's been a long time since I looked at them
and I can't remember the form. So I remember
that there were descriptive memoranda. I
remember a few things about them independent
of actually having them. But I can't remember
whether they were this form, how much the same
or how different these are.

Q. Let's look at the one that is at
page 008165, and under page 2 of that document
which is 8166 --

A. Yeah, uh-huh.

Q. -- this states, "A Phase II(b) dose
ranging trial began April 2000 in diabetic
neuropathic pain."

A. And what paragraph is this?

Q. Third.

A. Third?

Okay. Uh-huh.

Q. You recall knowing that when you were

doing your work, don't you?

A. I know it was in Phase II. I can't remember offhand whether it was II(a) or II(b) or whether there were two different phases.

Q. Were you aware that a go/no go decision for clinical efficacy was expected in June 2001?

A. No, I don't remember that. That's not to say I didn't know it; I just don't remember.

Q. Right.

Over on page 7 of this document, 8171, there's a discussion of phase II(a) studies, under clinical studies.

A. Uh-huh.

Q. Do you see that at the bottom?

And it states, "Phase II(a) studies suggest a trend towards analgesic effect at 75 BID, the maximum dose studied in this protocol."

Do you see that?

A. Yes, I see it.

Q. Does that refresh your recollection that the maximum dose used in the Phase II(a) study was 75?

A. It doesn't refresh my recollection. Part of the problem is I don't know what was included in

this later memorandum from the ones that I saw.
Q. I understand. But I'm simply asking you if it refreshes your recollection.
A. Well, I do remember the 75 micrograms by daily, yes.
Q. And then below that talks about, again talks about the Phase II(b) study beginning in April 2000 and ending in 2001. Would this refresh your recollection as to whether you had that information at any point in time in doing your work?
A. It doesn't refresh my recollection.
Q. You just don't recall one way or --
A. I just don't recall one way or --
Q. You recall having any information then about the number of patients who were anticipated to be included in the study?
A. No, I don't recall that either.
Q. Over on the next page, it says, "target profile."
The current status of ABT-594's profile --
(Interruption by the reporter.)
Q. "The current status of ABT-594's profile versus target profile is summarized in the table

below."

Do you see that?

A. Yeah.

Q. And then at the bottom the last attribute, it says, "low nausea slash vomiting. Probability low."

Do you see that?

A. Yes, I see it.

Q. Do you recall having that information during the period of time in which you --

A. No. I don't recall one way or another of having that information.

Q. Do you recall being told by anybody that the probability of achieving low nausea and vomiting with this drug was low?

A. No.

Q. Assuming this information was given to John Hancock, is it clear to you that John Hancock knew that the probability of achieving 594 profile with low nausea and vomiting was low?

MR. DAVIS: Objection. I caution you not to speculate.

THE WITNESS: Yeah, I can't speculate.

Q. Did Mr. Blewitt ever tell you that he knew

the probability of achieving low nausea and vomiting with the 594 was low?

A. No.

MR. DAVIS: Objection.

Q. Did you have an understanding apart from this document that the probability of achieving low nausea slash vomiting from 594 was low?

A. No, because I would have -- that would have raised a huge red flag for me.

Q. So this was information which if Mr. Blewitt had you'd expect him to tell you about, wouldn't you?

MR. DAVIS: Objection. You can respond.

THE WITNESS: I can't speculate.

Q. If it turns out this was in the descriptive memorandum that you saw, would you say you just missed it?

MR. DAVIS: Objection.

THE WITNESS: Again, it would be hard to miss it, but I don't remember this table, so one way or another.

Q. Well, let's assume that it was in there, assume for argument's sake that it was in there.

A. All right.

MR. DAVIS: Is that the question?
MR. WEINBERGER: No.
MR. DAVIS: Okay.
MR. WEINBERGER: That's just the predicate.
Q. Then would you have any explanation for your not noting that and dealing with that issue besides just missing it?
MR. DAVIS: Objection. You may respond.
THE WITNESS: If it was in there, I would have no real -- I would have no good explanation for not dealing with it.
MR. WEINBERGER: Okay. Let me see if I have anything else.
Q. Yeah.
There's another descriptive memorandum. All right. Look at the descriptive memorandum on 518 which is -- which begins at JH 008193.
A. 8193?
Q. Yes.
A. Okay.
Q. I want to ask you if we were trying to figure out what descriptive memoranda you got, without the benefit of having your files since they

were destroyed, what is your best estimate, given that you appeared to have first talked to Hancock about consulting in May and you put together a memo of your preliminary thoughts I think in June, as to when you got the descriptive memoranda?

A. It must have been before my preliminary thoughts because they were based on -- they were based on the knowledge of Abbott's drugs, which I at that point could have only gotten from a descriptive memorandum.

Q. So May or June?

A. Yeah, May or June.

Q. So if we found the descriptive memorandum, the most current one that Abbott provided Hancock in the time of May or June, it was likely that you saw that?

MR. DAVIS: Objection. You may respond.

THE WITNESS: Yes, it is likely that I saw it.

Q. Now, if there were changes to the memoranda that were done before you stopped your work, which I think was the end of July; is that right?

A. Yes.

Q. Would you have seen those as well you believe?

MR. DAVIS: Objection. You may respond.

THE WITNESS: I don't recall seeing any other memoranda except the ones I saw in the beginning.

Q. Okay. Now, over on the third page of the December -- fifth page of the descriptive memorandum --

MR. DAVIS: Which one?

Q. For 518. So that's at page 008197.

A. Uh-huh.

Q. Discussion of other companies that are targeting this mechanism.

A. Uh-huh.

Q. You see that there's one talked about marimastat by British Biotech?

A. Uh-huh.

Q. And that's the one that we've already discussed had some negative results, correct?

A. Yes.

Q. And that's what's reported here, correct, that there are negative results in pancreatic?

MR. DANIEL: Objection. You may respond.

THE WITNESS: Ask your question again. I was reading.

Q. Those results in part are reported here that there are negative results in pancreatic, correct?

MR. DAVIS: Objection. You may respond.

THE WITNESS: I can't remember the details of what the negative results were.

Q. And Abbott also disclosed to you, I think we discussed this before, that Abbott also disclosed that these compounds listed up in this box have joint side effects that would preclude their long term use.

MR. DAVIS: Objection. You may respond.

THE WITNESS: I don't know that Abbott discussed that with me.

Q. But you knew that, that was in some of the documents that we looked at before.

A. Yeah, then it must have --

MR. DAVIS: Objection. You can respond.

THE WITNESS: Then it must have come from the memoranda. Yes. I had no direct contact with Abbott.

Q. But you reported that in the interview

notes that you prepared for Abbott and for the experts. Do you recall that?

MR. DAVIS: Objection. You may respond.

THE WITNESS: Well, I can go back and look at the interview notes but I, you know, we can just say if it was in there, then apparently I knew it from somewhere.

Q. Okay.

A. And would it be likely from the descriptive memoranda.

Q. Okay. Now, this memorandum also says, "Abbott's timing to market is not optimal."

Now, based on your work on this compound, do you have any understanding as to what was meant by that?

Well, let me first ask you, do you agree with that, that Abbott's timing to market was not optimal?

MR. DAVIS: Objection. You can respond.

THE WITNESS: I have no way of really responding to that one way or another because I don't know what they mean by "not optimal."

Q. Well, over on the next page, 8198, under Marketing Overview, under the heading Side Effects,

in the middle, it states, "As the third or fourth MMPI to market, SE hurdles will be even higher for this compound"; that's side effect, right?

A. Uh-huh.

Q. As a critical go/no go decision point, the joint toxicity of this compound will be evaluated and expanded Phase I multidose study."

A. Again, because my memory doesn't inform me on this, I somehow think that this might not be in the original.

Q. Okay.

A. Original documents.

Q. So you don't have any recollection of Mr. Blewitt coming back to you and saying, you know, we got new information from Abbott on the 518 that we'd like you to look at?

MR. DAVIS: Objection. You can respond.

THE WITNESS: No. He didn't come back to me after the end of July.

Q. You were available as far as you understood to evaluate any new information that Mr. Blewitt got from Abbott --

A. Yeah, I was available, yes.

Q. -- if he thought it was important to do

so, right; you could have done that?

A. Well, if he thought it was important to do so, I don't know how to answer that; that would be speculation.

Q. No, no, no. I'm not -- I'm just asking you if there's any reason that you would not have been available to evaluate any new additional data he got on any of these compounds that he thought was significant?

A. I would have been available, yes.

Q. Over on the next page under Competition, the document states, "As the third or fourth MMPI to market" -- now, let me ask you this, just stopping right there -- were you aware in doing your work that at best case the Abbott compound would be the third or fourth MMPI to market?

MR. DAVIS: Objection.

THE WITNESS: You want me to answer or not?

MR. DAVIS: Yeah, you may respond if you know. I caution you not to speculate.

THE WITNESS: Okay. The only one I knew for sure was marimastat to my recollection.

Q. Well, marimastat, you believe marimastat

was coming to market?

A. Is the only one I knew that -- the only one I can remember I knew anything about, I'll put it that way.

Q. You didn't know it was coming to market; just you remember --

A. No.

Q. It says, "Strict go/no go criteria will determine if the MMPI can meet these hurdles." Were you aware of that?

MR. DAVIS: Objection. You can respond.

THE WITNESS: No, I wasn't. This stuff doesn't look familiar from the point of view it was in the first memo. So --

MR. WEINBERGER: Let me just look at my notes.

Q. Just so we're clear on this, from the time you had your call with Dr. Leonard until the time you were contacted by Choate, you had absolutely no involvement in this matter, correct?

A. I sent, after Dr. Leonard's, I wrote up my notes and sent them. And I can't remember whether Steve had responded to those, you know, saying thank you, I got them. I don't know. But beyond

that, I had no contact.

MR. WEINBERGER: Okay. And counsel, am I correct that it's your position that all work he did from the time that you contacted him until the present is as an expert consultant, non-testifying consultant?

MR. DAVIS: From the time he was retained as a non-testifying expert consultant, that work he has done for us is in that capacity.

Q. So you have no knowledge with respect to any issues in this case between the date of your interview with Dr. Leonard and your retention by Choate that you would expect to testify about at the trial of this case; is that correct?

A. That's not exactly correct. Gretchen Edson asked me for whatever documents I had and that was sometime before I talked to Brian.

MR. DAVIS: I object to the question actually. Please pause.

Q. She asked you to produce documents.

A. Yes.

Q. We've already discussed that.

A. Yes.

Q. But other than that?

MR. DAVIS: Objection. You can respond.

THE WITNESS: Other than, no.

MR. WEINBERGER: I have nothing further.

MR. DAVIS: You haven't asked him any questions about 773. I offer you the opportunity to do so if you wish.

MR. WEINBERGER: 773 is not in this case. Should the court grant your -- you've got a motion for leave to amend, which obviously means it's not in the case, otherwise you wouldn't need one. And should the court grant that motion, then we'll need to take appropriate discovery with respect to 773 as well as anything else that is the subject of the amendment. But I'm not going to be taking depositions about something that is not in your complaint.

MR. DAVIS: Okay. Abbott has taken discovery about 773 in this case already. And I offer you now the opportunity to question him about 773 if you wish to do so. I don't want to bring him back later so that you can further question him about 773 when it has been an issue in this case and you have the

VOLUME: II

EXHIBITS: See Index

UNITED STATES DISTRICT COURT

DISTRICT OF MASSACHUSETTS

- - - - - - - - - - - - - - - - - - x

JOHN HANCOCK LIFE INSURANCE COMPANY,
JOHN HANCOCK VARIABLE LIFE INSURANCE
COMPANY, and MANULIFE INSURANCE COMPANY
(f/k/a/ INVESTORS PARTNER INSURANCE COMPANY)

Plaintiffs Civil Action

v. No. 05-11150-DPW

ABBOTT LABORATORIES

Defendant

- - - - - - - - - - - - - - - - - - x

CONTINUED DEPOSITION of LYNN KLOTZ

Wednesday, May 16, 2007

9:42 a.m.

Donnelly, Conroy & Gelhaar, LLP

One Beacon Street

Boston, Massachusetts

Michelle Keegan, Court Reporter

Q. I will warn you I tend to pause midquestion
as well. Just be patient. It's not a rush.
A. I'll wait for you to do something like this
to suggest I answer.
Q. Thank you.
MR. DAVIS: Eric, I assume all of the
same stipulations also are in force?
MR. LORENZINI: That's correct.
Q. And if at any time you don't understand a
question, please ask me and I will rephrase it.
Dr. Klotz, as you'll recall at your
earlier deposition, you testified generally
regarding the investigation you undertook to gather
information about the drugs that were going to be
included in the research funding agreement. Do you
recall that?
A. Yes.
Q. I wanted to ask you specifically now about a
particular compound that was under consideration for
inclusion in that agreement; and that is ABT-773.
Do you recall conducting research regarding ABT-773?
A. Yes, I did. I don't remember -- I remember
virtually none of the particulars, but I do recall.
Q. Do you recall that ABT-773 was an

antibiotic?

A. Yes.

Q. And specifically, that it was a ketolide?

A. A ketolide, yes.

Q. A ketolide?

A. Yes.

Q. And you recall that ketolides are a derivative of macrolides?

A. Yes, I know that. Not from my memory from the 2000 investigation, but just from having recently reread the notes that you have, too.

Q. Are you referring to the notes that you prepared during your investigation back in 2000?

A. Yes. I sent the hand copy in part of your discovery. Those notes, yes.

Q. So you knew at the time of your investigation that ketolides were a derivative of macrolides?

A. Yes.

Q. And you knew that ketolides shared a similar mechanism of action to macrolides, correct?

A. Yes.

Q. In conducting your investigation regarding ABT-773, what documents did you receive from John

Hancock regarding that particular compound?

A. I was sent what you people call descriptive memoranda.

Q. Did you have another term that you used for those documents?

A. I can't remember. I don't recall using that term. I might have called them data sheets or something, but I can't recall.

Q. Did you receive any other documents from Hancock other than the descriptive memoranda?

MR. DAVIS: When you talk about documents, specific to 773?

MR. LORENZINI: Correct.

A. I don't know.

Q. You don't recall receiving them?

A. I don't recall.

Q. Did you receive more than one draft of the ABT-773 descriptive memoranda?

A. I don't think so.

Q. Did you receive any documents directly from Abbott regarding ABT-773?

A. No.

Q. You didn't receive any documents directly from Abbott on any of the compounds, correct?

A. I'm pretty sure I did not.
Q. What documents regarding ketolides or ABT-773 in particular did you receive from other sources or gather from other sources?
A. I gathered, not so much received, unless you consider an interview being received, from doing Web search, PubMed search, and I believe also a Dialogue Search, which is another database, I downloaded a number of abstracts on ABT-773.
Q. Are there any other sources that you used in your searches?
A. I had one interview, an expert interview.
Q. And was that with Dr. Moellering?
A. Yes.
Q. You didn't speak with any other experts regarding ABT-773?
A. No. It was pretty straightforward.
Q. I just want to go over these sources that you used to conduct the searches. The first one you mentioned was Pub Med?
A. Pub Med, yeah.
Q. Could you spell that out, please.
A. P-U-B, then capital M, E-D. It's a national database of medical and scientific journals.

A. Yeah. I haven't looked at exactly what I pulled up, but there could be scientific data, yeah.

Q. Are there any other databases you searched other than Pub Med and Dialogue Search?

A. I don't recall that I did.

Q. Did you conduct any more general Internet searches just using Google or some search engine like that?

A. I'm not sure now.

Q. Do you recall what search terms you used when you were researching ABT-773?

A. I certainly used "ABT-773" and pulled up a lot of papers. I can't say for sure, but I probably used "ketolide" and things like that. I don't remember the other search terms.

Q. Did you use "macrolide" as a search term?

A. I don't remember.

Q. In the course of your investigation, did you speak with anyone at Abbott regarding ABT-773?

A. We had a telephone interview, Steve Blewitt and me and James Leonard. And there were two other people from Abbott whose names I forget.

Q. Possibly Phil Deemer and Steve Cohen?

A. Yeah, I guess. I've been told afterwards

what the names were, but I've forgotten again.
MR. LORENZINI: This will be Klotz Exhibit 20.
(Exhibit Number 20 marked for identification)
Q. Dr. Klotz, you have before you what's been marked as Klotz Exhibit 20. It's titled "ABT-773 Descriptive Memorandum." It's dated in the title as May 2000, although in the lower left-hand corner footer there's a June 5, 2000 date.
Do you recognize this document?
A. I can't say that I specifically recognize the document because it's been so many years.
Q. Is it generally the same format as the descriptive memoranda that you were referring to earlier that you received from Hancock?
A. I understand that I reviewed descriptive memoranda for all the things in the package. I can't speak to its exact form because I just don't remember.
Q. Do you recall receiving any other version of the descriptive memorandum for 773 other than Exhibit 20?
A. No. I think only one version.

Q. You don't have any reason to believe that this isn't the version you reviewed?

A. No, I have no reason to believe that this isn't the version. This is likely the version.

Q. If you'll turn to page 4 of the descriptive memorandum. And if you'd look at the table towards the bottom, you'll see it has a listing of adverse events in a particular phase 2 clinical trial of ABT-773.

A. Uh-hmm.

Q. One of the adverse events listed is elevated liver function test.

A. Uh-hmm.

Q. And you'll see under the 100 milligram dose group it indicates 1 percent of the patients had elevated liver function test results and also 1 percent of the patients in the 200 milligram dose group?

A. Uh-hmm.

Q. Do you recall receiving that information from Hancock in the descriptive memorandum for ABT-773?

A. At this time I don't recall.

Q. Do you recall learning generally from your

independent research that there had been elevated liver function test adverse events in one phase 2 study of ABT-773?

A. Again, it's not recall, but it's more reconstructing from having read the notes recently because I knew I was going to be deposed. From that I don't remember seeing in the literature searches that I did anything about elevated liver function tests.

Q. But if it was in the descriptive memorandum, then you learned that information directly?

A. Yes, it's there.

MR. DAVIS: Hold on. Pause before you answer. Object -- Objection. You may respond.

A. It's there. I presume that I saw it.

Q. And it didn't raise any concerns for you?

A. Apparently not.

MR. LORENZINI: This one actually doesn't need to be marked. It was previously marked as Klotz Exhibit 7.

Q. Before we move on to Exhibit 7, I just want to ask you going back to the liver function test why did that not raise any concerns for you, the 1 percent elevated liver function test in the phase 2

study?

MR. DAVIS: Objection. I think he's already testified he didn't recall reviewing this information at that point in time. So I caution you not to speculate. But if you do recall, answer his question.

A. No, I don't recall. I could speculate, but he's cautioned me not to speculate, so I will not speculate.

Q. Referring back to what's been previously marked as Klotz Exhibit 7, I believe you testified last time that these were notes that you compiled and sent to Stephen Blewitt after your review of the descriptive memorandum for the various compounds.

A. Yes, I've seen them recently. I know they're my notes.

Q. Could you turn to page JH 002087. You'll see there's a heading there for ABT-773.

A. Uh-hmm.

Q. Does that section contain your initial comments and questions regarding ABT-773 based on your review of the ABT-773 descriptive memorandum?

A. I should read it first?

Q. Sure.

(Pause)

A. Yes.

Q. So after your review of the ABT-773 descriptive memorandum, you didn't have any other initial comments or questions regarding ABT-773?

A. I may have had others. I just chose to write some. I probably just chose to write some down.

Q. Were these the ones that you considered most significant to raise with Mr. Blewitt?

A. I can't say. I don't remember.

Q. Do you remember any other questions or comments or concerns you had after reading the descriptive memorandum on ABT-773?

A. No, I don't remember.

Q. You refer in your notes here to possibly consulting an expert like Stewart Levy.

A. Yeah, Levy. Yes.

Q. Who is Stewart Levy?

A. He's an infectious disease expert at Tufts University. I had, although I can't give you the details any more, some previous contact with him off and on.

Q. Had you ever discussed ketolides with him?

Q. And did you contact Andy Onderdonk in connection with your investigation of the Abbott compounds?

A. No, because I found other experts from the literature, so I didn't need his information.

Q. You have some other questions in your notes here regarding ABT-773. Did you get answers to those questions in the course of your investigation?

A. Without rereading every question, I think we took all what I thought were the relevant questions to Robert Moellering. And I had a very good interview with him.

Q. And you felt satisfied after your conversation with Dr. Moellering that your questions had been answered?

A. Yes.

MR. LORENZINI: That will be Exhibit 21.

(Exhibit Number 21
marked for identification)

Q. Dr. Moellering, you have before you what's been marked as Klotz Exhibit 21. Its's a document Bates-stamped JH 002212 through 2226. It appears to be a series of articles or abstracts.

A. Abstracts.

MR. DAVIS: I'm sorry. Did you refer to him as Dr. Moellering? That's okay.

MR. LORENZINI: Sorry about that. It hasn't happened yet.

Q. I apologize. Dr. Klotz.

A. I don't talk to myself.

Q. Dr. Klotz, are these abstracts that you located in your search of the databases regarding ABT-773?

A. Yeah. Looking at the first few, they're Pub Med searches.

Q. So these are just the results of your Pub Med search?

A. Well, I haven't looked at the ones in the back. Let me take a look.

MR. DAVIS: Take a moment.

THE WITNESS: Yes. Okay.

(Pause)

A. I see news wire releases and things like that in the back. I'm presuming they come from Dialogue, although I can't swear to it. I might have picked them up from something else that I don't remember.

Q. If you look generally through this document

that's marked as Exhibit 21, you'll see that there's some text that's in bold font.

A. Yes.

Q. Is that bold font that you added?

A. That is bold font that I added.

Q. And does that indicate the passages of the abstracts that you thought were particularly significant?

A. As I scanned through the documents, yes, that was my first take on what I might want to go back to and might be significant.

Q. And there's also some text that's in italics. Is that text that you added providing comments on the abstract?

A. Yes.

Q. And in your review of this literature, did it appear to you that ketolides were a promising class of antibiotics?

A. Yes, they looked quite promising.

Q. And in particular, did it appear that ABT-773 was promising?

A. Yes.

Q. On the second page of Exhibit 21 there's an abstract at the top regarding a compound named HMR

3647. And this is a drug that was under development by -- I'm not sure if I'm going to pronounce this right, but Hoechst, Marion Roussel?

A. Hoechst, yeah, which I think they go by the name Aventis. That's easier to pronounce.

Q. Do you recall later learning that this compound HMR 3647 later acquired the name Ketek?

A. Yes, I recall that from reading my notes. Yes.

Q. And that was after Hoechst became Aventis that the name of the compound changed to Ketek?

A. I don't know when the compound name changed.

Q. Okay. In your commentary there in italics you say, "Abbott doesn't list this," "this" meaning HMR 3647, "in its key emerging competitors even though this is a November 1999 article."

Do you recall clarifying later that Abbott actually had listed that compound?

A. Under the name Ketek?

Q. Correct.

A. Well, as you can see, as at that point I'm still trying to figure out exactly what compound that was. And I do know from reading my later notes that that was Ketek, yes.

Q. So Abbott hadn't hidden the existence of that competitor compound?

MR. DAVIS: Objection. You can respond.

A. No.

Q. And --

A. As far as I know.

Q. If you look back at the descriptive memorandum that was marked as Exhibit 20 -- Go ahead.

(Pause)

Q. If you look at the last -- final page, please. You'll see in the descriptive memorandum there that Ketek is listed?

A. Yes. At this point I was trying to get my bearings on these things.

Q. I understand. If you look at the bottom of page 2216 of Exhibit 21, there is an abstract there specifically regarding ABT-773. And you've bolded the last line of that abstract which says, "ABT-773, therefore, shows promising in vitro activity against macrolide-susceptible as well as -resistant pneumococci."

A. I should be able to pronounce that right off the top of my head, but you have me there. Yeah,

pneumococci.

Q. So this was a promising study for you that indicated ABT-773 was a promising compound?

A. Yes.

Q. And you noted there in italics, "Confirms Abbott's statements." Is that a reference to the fact that this abstract confirmed the statements Abbott had made in the descriptive memorandum?

MR. DAVIS: If you recall.

A. Yeah, I presume so. But again, from looking back at the descriptive memorandum now, I'd say yes. It's so long ago. It's hard to say exactly what I was referring back to then.

Q. But those are your italicized comments?

A. Yes, they certainly are.

Q. At the top of Exhibit 21 you've included a comment that looks like there's three stars and then it says, "For Steve to read."

A. At the top, yeah.

Q. And some of the abstracts if you look through have three stars to the left of the title. Was that an indication of particular abstracts that you intended to send to Steve Blewitt?

A. Well, first, I sent them all because that's

where you got them from, in discovery. I can't
remember exactly whether those three stars
correspond to this. I would presume so.
MR. DAVIS: Don't speculate. If you
know.
A. Okay. I don't know.
Q. But you did send this entire set of
abstracts to Steve Blewitt?
A. Yes, yes.
(Exhibit Number 22
marked for identification)
Q. Dr. Klotz, you have before you what's been
marked as Exhibit 22. It is an e-mail from you to
Stephen Blewitt dated July 4, 2000 with an
attachment titled "Abbott's ketolide antibiotic."
Is this an e-mail that you sent to
Stephen Blewitt with a summary of the results of
your literature search?
A. I don't know the date on the rest of this,
but if it's the same date, then yes.
Q. And is this a selection of the abstracts or
portions of abstracts that you thought were most
relevant for Stephen Blewitt to review?
A. I call them example articles. Beyond that,

I don't think I should speculate.

Q. Do you recall that you concluded based on your literature search that ABT-773 might be the most promising of Abbott's drugs in the -- that were being considered for the research funding agreement?

A. Again, I recall from my rereading the discovery notes a few days ago, the answer is yes.

Q. And you wrote that in your e-mail to Mr. Blewitt here?

A. Yes, yes, yes.

Q. You also note in your e-mail that, "ABT-773 may even achieve the greater than $1 billion market share they project since Aventis publicly projects $1 billion for its ketolide Ketek just on the market." And you also note that, "Abbott's is not far behind, and they have superior properties"?

A. Yes.

Q. Was that, in fact, your conclusion based on the review of the literature, publicly available literature?

A. Yes.

(Exhibit Number 23 marked for identification)

Q. Dr. Klotz, you have before you what's been

THE WITNESS: You want me to respond?

MR. DAVIS: Yes, if you can.

A. Because everything I supplied to Hancock were in the discovery notes as written materials.

Q. What do you mean by "in the discovery notes"?

A. We've been calling it the big black book. It's the materials which he has and you have which have these labels on the bottom.

Q. And you'll note this document, Exhibit 24, does have that Bates label. It's just for some reason the first page it doesn't appear on the bottom, but it does have a JH 000767 stamp.

A. But that doesn't mean I supplied it. I'm just pointing out, the things in the discovery notes that I see, my stuff has the JH labels. So I haven't seen this article.

Q. Did you conduct any searches during your investigation of the Medscape.com Website?

A. I don't recall.

(Exhibit Number 25
marked for identification)

Q. Dr. Klotz, the court reporter has marked as Exhibit 25 a document that begins with Bates number

JH 000655. It's titled "Abbott's Ketolide Antibiotic (ABT-773)," and it includes some handwritten notes. Do you recognize this document?

A. Yes.

Q. What is it?

A. What is it?

MR. DAVIS: If you know.

A. I can read what it is. It is a list of people we might interview. It's some of the questions as they were being developed at that point that we might ask them.

Q. And are these your handwritten notes?

A. No.

Q. Do you know whose notes they are?

A. No.

Q. If you look at the upper right-hand corner of the exhibit, one of the handwritten notes says, "Toxicity," question mark, and it's crossed out. Did you ever have any conversations with Stephen Blewitt regarding any toxicity issues related to ABT-773?

A. I don't recall.

Q. Did you ever have any discussions with Dr. Moellering regarding whether there were any

toxicity issues associated with ABT-773 or with ketolides in general?

A. My complete interview with Moellering is in your documents. I would have to review it.

Q. If you had discussed that issue with Dr. Moellering, it would have been in those notes?

A. It would be in those notes, yes.

(Exhibit Number 26 marked for identification)

Q. Dr. Klotz, the court reporter has marked as Exhibit 26 a document that has been produced by John Hancock in this case entitled "Pertinent Information On Interview Candidates." Is this document, Exhibit 26, something that you compiled?

A. Let me just look through really quickly.

(Pause)

A. Yes.

Q. And is this information you prepared in preparation for interviews with experts regarding the compounds?

A. It's information along the way to conducting interviews.

Q. If you'd turn to page JH 002195.

A. Okay.

Q. You'll see there's a heading there "ABT-773 Ketolide Antibiotic for Resistant Bacteria."

A. Yes.

Q. Next to that heading there's a parenthetical that says, "This is technically straightforward. Only one interview." Is that your comment?

A. That's my comment, yes.

Q. And why did you believe that ABT-773 was technically straightforward?

A. This is going to take more than a short answer.

MR. DAVIS: Go ahead.

A. In the first place, clinical trials for antibiotics are straightforward compared to clinical trials for other things. If it's a lung infection, you just take a sputum sample and see if the bacteria is gone. The patient gets better. That's a fairly straightforward clinical trial endpoint.

At the time I did this work this had already gone through phase 2 with both Abbott and external literature saying it looks very promising.

So we felt the only thing we had to do was just make sure that some expert, somebody who knows the field out there, either confirms or denies

what we knew at that point or what we thought we knew at that point.

Q. And you list on this page of Exhibit 26 two primary -- two groups of primary interview candidates and then an alternate. You mentioned before that Stewart Levy didn't have time.

A. Yeah.

Q. The next group of primary interview candidates listed here are someone named T. Schulin, C.B. Wennersten, R.C. Moellering, Junior and G.M. Eliopoulos.

A. Your guess is as good as mine.

Q. On the pronunciation, you mean?

A. Right. On the pronunciation, yes.

Q. But those are the individuals listed there?

A. Yes.

Q. And you ended up interviewing Dr. Moellering. How did you choose Dr. Moellering from among the four individuals who are listed here on this page of Exhibit 26 as authors of --

A. Specifically, I don't recall.

Q. Did you try to contact any of the other individuals listed here other than Dr. Moellering and Dr. Levy?

A. I don't recall.
Q. Do you know if it was less than a half hour?
A. I would have to speculate.
MR. DAVIS: Don't. If you know. Don't speculate.
Q. Don't speculate.
A. Okay.
Q. The introductory statement here on this exhibit also states, "John Hancock is willing to give you an honorarium of $150 for your help."
A. Uh-hmm.
Q. Did you offer an honorarium to all the experts that you contacted?
A. Yes.
Q. And did Dr. Moellering accept your offer of an honorarium?
A. I can't say whether he explicitly did or not, but I did send honorarium checks to everyone.
Q. So you sent a $150 check to Dr. Moellering for his time?
A. Yes.
Q. Did you just have one phone call with Dr. Moellering?
A. Yes.

Q. And was it a scheduled call or was it just
impromptu, you called him up and started talking
about the substance?
A. I don't recall.
(Exhibit Number 27
marked for identification)
(Pause)
Q. Dr. Klotz, the court reporter has marked as
Exhibit 27 an e-mail dated July 21, 2000 from you to
Stephen Blewitt with an attachment entitled "Robert
Moellering interview on" --
A. That's pronounced "colchicine," but it's
wrong. It's a pasting error.
Q. Just for the record, I'll finish.
The title is "Robert Moellering
interview on colchicine-site binding agents."
You're clarifying that's a mistake.
Is this, in fact, your notes of an
interview with Robert Moellering regarding
ketolides?
A. Yes.
Q. And in fact, if you look at the upper
left-hand corner of the attachment to Exhibit 27, it
does indicate there correctly "File:ketolides-

Moellering"?

A. Yes.

Q. So Exhibit 27 is your e-mail to Stephen Blewitt attaching your notes of your interview with Dr. Moellering regarding ketolides?

A. Yes.

Q. And if you look down at the heading "Interview," the subheading on the first page of the attachment, it says, "The interview summary below is typed from handwritten notes and memory shortly after the interview, and is therefore subject to error in details normal to this process."

Do you recall how soon after your interview with Dr. Moellering you typed up your notes?

A. Specifically, I don't recall.

Q. But soon after?

A. I would have to speculate, but "soon" is a fair characterization, I guess.

Q. Well, you say here in the summary "shortly." You use the term "shortly." You'd agree it was shortly thereafter?

A. (No verbal response)

Q. Is that --

A. Yeah. You might want to define "shortly" a little more clearly, but I try to do it as fast as I can.

Q. And your typewritten summary here was based on handwritten notes that you took during the course of the telephone conversation?

A. Yes.

Q. You state in your summary here that it's "subject to error in details normal to this process." Have you reviewed this summary recently, Dr. Moellering, in preparation for your deposition?

MR. DAVIS: Dr. Klotz.

MR. LORENZINI: I'm sorry.

A. You've promoted me.

Yes, I reviewed it. I reviewed this a few days ago, yeah.

Q. And did you see -- Did you notice any errors in your summary?

A. I did not notice any.

Q. Turn to page 2 of the summary, please. The second to last paragraph states, "Abbott's ketolide has more promise than Aventis'. I'm talking relative here. Ketolides have pluses and minuses because they are modified macrolide antibiotics."

Do you recall that Dr. Moellering told you that Abbott's ketolide has more promise than Aventis's ketolide, Ketek?

A. I don't recall it today, but I see that I wrote it here.

Q. So Dr. Moellering did inform you of that based on your notes here?

A. I presume so, yes, since I don't recall.

Q. Do these notes capture all of the -- all aspects of your discussion with Dr. Moellering?

MR. DAVIS: Objection. You can respond.

A. As far as I remember, yes.

Q. You don't recall discussing any other topics with him?

A. No, I don't recall. And I read the notes...

Q. And they appear accurate?

A. They appear accurate given that I don't have a direct recollection of the original interview.

Q. And just to be clear, in these notes the italicized text indicates your questions to Dr. Moellering?

A. Yes.

Q. And the nonitalicized text represents Dr. Moellering's comments?

A. My write-up of his comments, yes.

Q. Do you recall asking Dr. Moellering at the end of your conversation if there was any important issue that you hadn't discussed or important question that you hadn't asked?

A. I don't recall directly, but I often end an interview with that.

Q. And if you'll turn to the third page of the attachment, you'll see that in italics it states, "Is there an important issue we haven't discussed or important question I haven't asked?" And then it has as the answer, "No. I think we've pretty much covered it."

Does that refresh your recollection that you followed your standard procedure and asked Dr. Moellering that question during your -- at the conclusion of your interview with him?

A. Again, my recollection of exactly what happened in 2000 is almost nothing. But this is consistent with the kind of thing I would ask. And I presume I got the answer correct.

Q. The answer as represented here?

A. As represented here, yes.

Q. So at the end of your conversation

Dr. Moellering didn't have any further issues that he thought were important?

MR. DAVIS: Objection. You can respond.

A. I presume that's what he meant.

Q. Do you recall that Dr. Moellering believed that it was possible for Aventis's ketolide to reach $1 billion in sales?

A. I'd have to reread what he said in here. If you'd give me a few minutes.

Q. Sure. I think you'll want to direct your attention -- Feel free to look at the entire document, but you'll probably want to direct your attention to the second page of the attachment, about three quarters of the way down.

A. Second page is which number, 995 --

Q. 2996.

A. 2996. Okay.

(Pause)

A. Yes, I see that.

What was the question again?

Q. Do you recall that Dr. Moellering told you that he believed it was possible under certain circumstances for Aventis's Ketek to reach $1 billion in sales?

MR. DAVIS: He's asking you your recollection as opposed to what's written in the document.

A. I have no recollection.

Q. But you believe what's written in the document in response to your question on that subject is accurate?

A. Yes. There were some ifs in there. Some things had to happen for that to happen, such a large dollar amount.

Q. Understood. Did Dr. Moellering say that those -- Did he assign any probability to those contingencies?

A. I would say no, because if he had I certainly would have put it in the notes because it would have been useful quantitative information.

Q. Your notes here on this same page, 2996, in italics state, "(Abbott's phase 2 data indicate a 92 percent effectiveness (overall eradication) against H. influenzae. How does this compare with erythromycin?)"

A. Uh-hmm.

Q. Did you do anything to follow up on that question?

A. I don't recall.

Q. Do you recall if you asked Abbott that question?

A. I don't recall. We'd have to get into that interview.

Q. If you had asked Abbott, it would be reflected in your notes of your interview with John Leonard?

A. I presume. Again, it's memory from seven years ago.

Q. Right. In your interview with Dr. Moellering you didn't discuss any heart issues associated with antibiotics?

A. No.

Q. You didn't discuss any QTc prolongation issues?

A. No.

Q. And did you discuss any liver toxicity issues?

A. No.

Q. You were aware that there had been QTc prolongation issues associated with some Quinn lines at this time, were you not?

A. I don't think I was aware of that. I don't

recall being aware of that.

Q. You don't recall that that was widely known?

MR. DAVIS: Objection. You can respond.

A. I don't recall.

Q. Do you recall that there were QTc issues associated with some macrolides?

MR. DAVIS: Objection.

THE WITNESS: Do you want me to answer?

MR. DAVIS: If you know.

A. It's I don't recall again.

(Exhibit Number 28 marked for identification)

Q. Dr. Klotz, the court reporter has marked as Exhibit 28 an article entitled "The Changing Face of Antihistamines and Cardiac Adverse Drug Reactions: A Clinical Perspective." This is not a document produced by Hancock.

I'd like to direct your attention to the first page. There's a heading entitled "Early pointers."

A. Yes.

Q. And I'm just going to read for the record, and you can read along, the first couple sentences there.

It states, "An early pointer to such unexpected side effects in fact came from antibiotics.

"A wide array of this class of drugs is being used in our country for the treatment of an equally wide variety of infections, but the lion's share goes to ambulatory therapy for community acquired respiratory tract infections where macrolides have deservedly made their mark all over the world.

"The prototype macrolide, erythromycin, which has been in use for nearly half a century, came under fresh scrutiny when certain cardiac side effects, such as delayed ventricular repolarization characterized by prolonged QTc interval, a precondition for the development of fatal ventricular tachycardias, were reported. The incidence increased on coadministration with other drugs with a similar propensity."

There's a footnote 2 there. If you'll turn to the last page of the document, you'll see that footnote 2 refers to a 1994 article.

A. Uh-hmm.

Q. Does this refresh your recollection that as

early as 1994 it was known that certain macrolides, including erythromycin, were associated with QTc prolongation?

MR. DAVIS: Objection. You haven't pointed out this document is from a publication in the country of India, number 1, if I read this correctly. If you know.

A. No, I don't know. I mean, I have no knowledge of this document or the other one, the 1994 one.

Q. You don't recall that in 1994 or sometime prior to 2000 that erythromycin was reported to have some QTc prolongation issues associated with it?

MR. DAVIS: Objection. You can respond.

A. I don't recall.

Q. Dr. Klotz, do you receive a publication called MedWatch from the FDA?

A. No.

Q. Are you familiar with the publication?

A. I've heard of it.

Q. Is it a publication widely subscribed to by doctors?

A. I don't --

MR. DAVIS: Objection.

A. -- know.

(Exhibit Number 29
marked for identification)

Q. Dr. Klotz, you have before you what's been marked as Exhibit 29. It's a MedWatch publication titled "Summary of Safety-Related Drug Labeling Changes Approved by FDA." It's dated June 2000.

And if you'd turn to page 6 of the document.

A. Uh-hmm.

Q. You'll see that there is a change to the drug labeling of the drug clarithromycin.

A. Uh-hmm.

Q. Are you familiar with clarithromycin?

A. No.

Q. You don't know -- Strike that.

Are you familiar with the term "Biaxin"?

A. No.

Q. So you didn't -- You are not aware that clarithromycin, also known as Biaxin, is a macrolide antibiotic?

A. No, unless I read it somewhere in my recent notes and forgot it.

Q. Are you familiar with any -- the names of

any macrolides?

A. Well, erythromycin is a macrolide. I'm obviously familiar with that. It's a common antibiotic.

MR. LORENZINI: We'll mark Exhibit 30.

(Exhibit Number 30 marked for identification)

Q. Dr. Klotz, you have before you what's been marked as Exhibit 30. It's an article from the European Journal of Clinical Pharmacology. It states that the date is received October 4, 1999; accepted in revised form, 13th of January 2000. Apparently it was published in 2000.

The title of this article is "QT Interval Prolongation By Noncardiac Drugs: Lessons To Be Learned From Recent Experience."

MR. DAVIS: Objection. You can respond.

There's a question?

Q. Are you familiar with the publication European Journal of Clinical Pharmacology?

A. No.

Q. If you'd look on page 2 of the article, under the heading "Classes of drugs and mechanisms underlying QT prolongation," you'll see the first

sentence states, "Through a MedLine search for literature published from 1985 through 1998 using the MESH terms," quote, "'long-QT syndrome - chemically induced', we retrieved 391 records."

And then if you look at the last sentence of that paragraph, it states, "Apart from antiarrhythmics, the largest numbers of cases within single classes refer to antopsychotics, histamine, H1 receptor antagonists and macrolides."

And then if you'll turn to page 3, you see that there's a chart representing results of a search for articles regarding QTc prolongation, and towards the bottom of that chart you'll see an indication that there were 32 articles regarding QTc prolongation associated with macrolides.

A. I see it, yes.

Q. Does that refresh your recollection that it was publicly known that there were QTc issues associated with some macrolides --

MR. DAVIS: Objection.

Q. -- as of 2000?

MR. DAVIS: Objection. If you know.

A. I was unaware of QT problems with Abbott's 773 and other macrolides and ketolides. I'm just

unaware.

Q. Ketolides is not a macrolide, you understand? It's a derivative?

A. I understand.

Q. And these articles don't discuss ABT-773, just to be clear?

A. Yes, I understand.

Q. But you weren't -- You weren't aware of the public -- articles in the public domain regarding QTc prolongations associated with some macrolides?

MR. DAVIS: Objection. You can respond.

A. I was unaware of any QT problems associated with Abbott 773 and other ketolides or macrolides, so I never did a lit search for QT as a Pub Med search term, a MedLine search term.

Basically, MedLine and PubMed are the same thing.

Q. Presumably Dr. Moellering would have been familiar with QTc prolongation issues associated with certain macrolide, correct?

MR. DAVIS: Objection. Calls for speculation. You can respond.

A. I don't know is the only answer I can give.

Q. He is an expert on macrolides and other

antibiotics, correct?
A. Yes, he is.
Q. If anyone would know, one would think he would know?
MR. DAVIS: Objection.
A. I don't know. I can't speak for him. And it is speculation.
Before we do this can I just take a bathroom break? I want to talk to Brian a little bit, too.
Q. That's fine. We don't have too much more.
(Recess taken)
Q. Dr. Klotz, I've handed you what was previously marked as Klotz Exhibit 15. It's an e-mail dated July 28th, 2000 from you to Stephen Blewitt with attached document entitled, "Telephone interview with Abbot conducted by L. Klotz, consultant, and S. Blewitt."
I believe you testified last time that this e-mail attached your notes of your interview with John Leonard at Abbott?
A. Yes.
Q. And if you'd turn to the second page, you'll see there's a heading ABT-773.

development, yeah.

Q. You were more involved in business issues than --

A. In business issues, yeah.

Q. You mentioned before the only macrolide antibiotic that you are aware of is erythromycin? That's the only one that you can think of?

A. I suppose if I looked at a big list I might be able to pick a few more out, but erythromycin is the obvious one, yeah.

Q. You don't have the expertise to determine what levels of adverse events in clinical or -- clinical tests regarding antibiotics are significant enough to raise development concerns, do you?

MR. DAVIS: Objection. You may respond.

A. If I didn't feel I had the expertise and I needed this kind of quantitative information, I'd go get it.

Q. But you don't have it personally?

A. No, I don't have it off the top of my head. No.

Q. You understand that with any compound under development there's always uncertainties regarding safety issues, efficacy issues, commercial

prospects?

A. Yes.

MR. DAVIS: Objection. You may respond.

A. Yes. I certainly understand that.

Q. And it's not unusual for a drug in development to, for example, show some adverse events during the testing phase, various types of adverse events?

MR. DAVIS: Objection. You can respond.

A. Yeah, it happens. I mean, not unusual -- I don't know exactly how I want to calibrate it, but yes, it does happen. There are adverse events.

Q. And that's not necessarily a barrier to regulatory approval of the drug, correct?

MR. DAVIS: Objection.

A. Yeah, it's not a barrier. It depends in part on what the drug is being used for. For example, cancer drugs you can get away with some pretty nasty stuff because you have a very nasty disease.

Q. So you really have to look at the specifics of exactly what the adverse event data is and what the compound is and what the indication is?

A. Yes.

Q. Any knowledge at all?

MR. DAVIS: Objection. You can respond.

A. I know what it means. It has something to do with prolonged heartbeats and things like that. Beyond that, I have no expertise.

Q. That's the extent of your knowledge, basically?

A. That's the extent of my knowledge.

Q. Do you have any expertise in liver toxicity?

MR. DAVIS: Objection. You can respond of the.

A. I probably know a little bit more about liver toxicity or had in the past, not that I'd be able to produce the language right here. I'm aware of liver toxicity with -- almost all drugs have some degree of liver toxicity.

Q. It's not uncommon?

MR. DAVIS: Objection.

A. It exists. "Not uncommon" is maybe a characterization that I'm not prepared to go -- to say. That's all.

Q. But even for drugs on the market --

A. Yeah.

MR. DAVIS: Let him finish the question,

information. That's what consultants like I do all the time is if there's something I'm aware of but don't have expertise on or a high degree of knowledge on, I go out and get the knowledge.

Q. Your literature searches on ABT-773 showed that ABT-773 had great promise in activity against bacteria that were resistant to other antibiotics, correct?

A. Yes.

Q. So that confirmed what Abbott was telling you, did it not, regarding the ability of ABT-773 to obtain a resistance claim, correct?

MR. DAVIS: Objection. You can respond.

A. Yes, it confirmed -- The literature search confirmed what Abbott had said.

Q. And your literature search didn't reveal any concerns regarding side effects associated with ketolide, did they?

A. No. I didn't specifically look for side effects.

Q. But you did generally look for information regarding ketolides, correct?

A. Yes. More specifically, Abbott 773.

Q. But also, I think, as we saw in Exhibit 21,

would have found those articles if you -- other than if you -- other than using "ketolide" as a search term?

MR. DAVIS: Objection.

A. This is all speculation at this point.

MR. DAVIS: Don't speculate. If you know, you can respond.

A. I don't know.

Q. I'm just asking based on your knowledge of these databases, how they operate, how the searches were --

MR. DAVIS: Same objection.

A. Yeah, same objection. I make one sort of general comment, if you type in one key word you might pull up a few hundred references.

I think in this case -- Again, this is speculation. It's the way I work.

MR. DAVIS: Don't speculate. He's entitled to what you know. If you don't know, you don't know.

THE WITNESS: This is the way I do databases. A general question I can answer, not a specific.

Q. Let me ask you generally, is Exhibit 21 the

entire set of abstracts that you located when you
did your search of the databases?
A. I can't recall.
Q. There might have been others?
A. There might have been others, yes.
Q. But you don't recall learning anything in
your abstract search regarding any concerns
regarding heart or liver issues with ketolides,
correct?
A. I don't recall seeing that, no.
Q. And Dr. Moellering didn't inform you that
there were any heart or liver issues with ketolides,
correct?
A. I don't recall directly, but from looking at
my interview notes, then he did not inform me.
Q. If Abbott was targeting as of the time you
did your research -- if its goal was to achieve once
a day dosing, you would understand that there would
be some uncertainty, that that's a goal, not a
certain outcome?
MR. DAVIS: Objection.
A. I understand now. I don't recall what I was
thinking back then.
Q. Do you recall -- Were you thinking at all

about dosing issues back then?

MR. DAVIS: Objection.

A. I don't recall.

Q. So you don't recall thinking one way or the other about the dosing for ABT-773, whether it be once a day or twice a day?

A. In general, I understand issues about dosing. I don't recall having -- I just don't recall to what extent I may or may not have considered those back then.

Q. And Steve Blewitt didn't ask you to look into the dosing issues on ABT-773?

A. I don't recall that he did.

Q. And the -- We saw in one of the exhibits, the descriptive memorandum, that there was a phase 2 test that showed 1 percent elevated liver function test results?

A. Yes, I remember that from just reading it now.

Q. That didn't cause you any concern?

A. 1 percent doesn't seem like a lot for me.

Q. It's not unusual for there to be some percentage of patients with elevated liver function test results?

MR. DAVIS: Objection. You can respond.
A. I don't want to speculate about not unusual or usual about a certain level.
Q. But that disclosure didn't cause you any concern?
A. Again, looking at it now and since I did follow it up, I presume it did not cause any concern back then.
Q. You mentioned in response to Mr. Davis's questions you would have been concerned if Abbott had known that there were likely to be delays of ABT-773 in the launch. You know that there's always uncertainty when a drug is being developed about the launch date, correct?
MR. DAVIS: Objection. You may respond.
A. Yes.
Q. That can always be set back?
MR. DAVIS: Objection.
A. Yes.
Q. And so if Abbott was projecting a launch date consistent with what had been disclosed to you, even if there was some uncertainty on that, as there always is, that wouldn't cause you concern if Abbott had, in fact, been projecting the same launch date

that was disclosed to you?

MR. DAVIS: Objection. You can respond.

A. I think if the launch date were postponed I would want to ask the question why. There might be a perfectly natural reason for doing it, but it might bring up some concern that would need further investigation.

Q. Were you told the launch date for ABT-773?

A. No. I was -- Well, I don't know if I was told, but given the way it was moving through clinical trials, I have knowledge of how long things usually take. These are fairly straightforward clinical trials. I could put my own estimate on it.

Q. Right. In Exhibit 20, if you look at that, there is mention of a launch date. Are you aware that Abbott subsequently provided Hancock with an updated version of this descriptive memorandum with an updated launch date?

A. At the time of my project and afterwards, no. I'm aware now.

Q. And after Hancock received that updated descriptive memorandum with a new launch date, they didn't forward that information to you?

MR. DAVIS: Objection.

A. After I supplied the report on the interview, my work was done with Hancock.

Q. So the answer is no?

A. The answer is no. Yes.

Q. And were you aware that Hancock subsequent to your work on the project received an annual research plan from Abbott that disclosed that dosing would be 150 milligrams BID or QD depending on the severity of the indication?

A. No, I wasn't aware. I did not receive any information.

Q. And they didn't ask you to do any sort of reanalysis based on that new information?

MR. DAVIS: Objection.

A. No.

MR. LORENZINI: I have no further questions.

MR. DAVIS: No further questions.

(Whereupon the deposition was concluded at 11:58 a.m.)

KLOTZ DEPOSITION EXHIBIT 1

D'S EXHIBIT FP

Lynn C. Klotz, PhD
71 Winslow Avenue
Somerville, MA 02144

May 1, 2000

John Hancock Life Insurance Company
John Hancock Place
200 Clarendon Street
Boston, MA 02117
Attention: Bond and Corporate Finance Group

RE: General biotechnology and pharmaceutical investments consulting

Dear Sir or Madame:

In connection with our possibly being retained to provide consulting or other services ("Consulting Services") to John Hancock Life Insurance Company, its affiliates and/or managed accounts (together, "Hancock") in connection with your evaluation of biotechnology and pharmaceutical investments (the "Transaction") with various companies (the "Company"), we may receive information (the "Confidential Information"), whether written, oral or otherwise, from Hancock, the Company or their respective employees, representatives or advisors regarding the Transaction or the business, operations and/of assets of the Company. The term "Confidential Information" shall also include all documents, material, analyses, compilations, studies or other documents or records prepared by us which contain, are based on or otherwise reflect Confidential Information. The term "Confidential Information" shall not include (i) information which is now in or hereafter enters the public domain through no action on our part; or (ii) information which we can demonstrate was in our possession prior to the time of disclosure and which was not acquired by us directly or indirectly from Hancock on a confidential basis.

We agree that the Confidential Information will be kept strictly confidential and will be used by us solely for the purpose of providing Hancock with the Consulting Services, and will not be used for any other purpose.

We agree that, without Hancock's prior written consent, the Confidential Information will not be disclosed by us, in whole or in part, to any person or entity other than those of our officers, employees and affiliates who need to know such information for the purpose of providing the Consulting Services and who have agreed to be bound by the provisions hereof. We agree that our officers,

employees and affiliates receiving the Confidential Information will be bound by our agreements hereunder, and we agree to be responsible for their actions, uses and disclosures as if they were original parties hereto.

We agree that we will not, and will direct our officers, employees and affiliates not to, disclose to any person the fact that the Confidential Information has been made available to us or to Hancock or that discussions or negotiations are taking place between Hancock and the Company concerning the Transaction or any terms, conditions or other facts with respect to the Transaction, including the status thereof.

We will promptly return to Hancock, upon its request or at the conclusion of the Consulting Services, all Confidential Information.

If we become legally compelled to disclose any of the Confidential Information, we agree to provide Hancock with prompt notice so that Hancock or the Company may seek a protective order or other appropriate remedy. If such protective order or other remedy is not obtained, we agree to furnish only that portion of the Confidential Information which is legally required and we will cooperate with Hancock or the Company, as the case may be, to obtain a protective order or other assurance that confidential treatment will be accorded the same.

We acknowledge and agree that none of Hancock, the Company, its affiliates or any of their respective directors, officers, stockholders, employees, representatives or agents is making any representation or warranty, express or implied, as to the accuracy or completeness of the Confidential Information, and none of such parties will have any liability to us or any other person resulting from the use of the Confidential Information by us or any of our employees, officers or affiliates.

We agree that any breach of this agreement may cause Hancock or the Company irreparable harm. We understand and agree that money damages would not be a sufficient remedy for any breach of this agreement by us or our employees, officers or affiliates and that Hancock and the Company shall be entitled to specific performance and injunctive or other equitable relief as a remedy for any such breach or threatened breach. Such remedy shall not be deemed to be the exclusive remedy for a breach of this agreement by us or our employees, officers or affiliates, but shall be in addition to all other remedies available at law or in equity to Hancock or the Company. We agree to indemnify and hold Hancock harmless in the event we breach our agreements contained in this agreement.

We agree that unless and until we execute an agreement for the Consulting Services with Hancock or the Company, as the case may be, neither Hancock nor the Company shall be under any legal obligation of any kind to us with respect to the Consulting Services by virtue of this agreement except for the matters expressly agreed to herein.

This agreement shall be governed by, and construed in accordance with, the laws of the Commonwealth of Massachusetts, without regard to the conflicts of law principles thereunder.

Very truly yours,
Lynn C. Klotz

By:

Name: Lynn C. Klotz
Title: Consultant

KLOTZ DEPOSITION EXHIBIT 2

D'S EXHIBIT 546

From: Lynn C. Klotz [LynnKlotz@compuserve.com]
Sent: Friday, June 02, 2000 10:06 AM
To: Blewitt, Stephen
Subject: my cv and thoughts about strategy

Attached is my cv, in case you haven't seen it before.

Also, your idea about financing baskets of drugs, and that combined with options to convert to stock targeted to companies of sufficient size and in need of mezzanine or post-mezzanince financing seems like the base of a good strategy to me. We should discuss why or why not some active strategy like this one can be pursued.

-- Lynn

PENGAD 800-631-6989 EXHIBIT
DW 2
KLOTZ 11-16-06

CONFIDENTIAL
JH 003089

CURRICULUM VITAE

Lynn Charles Klotz

Mailing Address:
71 Winslow Avenue
Somerville MA 02144
Tel: 617-623-6375
Fax: 617-623-6372
E-mail: lynnklotz@compuserve.com

Selected Professional Experience:

- Member of four-person team consulting with the President and Senior Administration of Mississippi State University to provide a strategic plan for their Life Sciences Institute, June 1999-March 2000.
- Professor and Course Director, Harvard University Summer Executive Program, for the course "Biotechnology and Modern Drug Discovery and Development," July 1997, 1998
- Special Consultant in Technical Strategy to Codon, Inc. and Oncor, Inc., 1992 - 1998
- Chair, Subgroup on Industry Concerns, Federation of American Scientists Working Group on Biological Weapons Verification
- Member, Founding Team and Scientific Advisory Board, Codon, Inc. 1994 - 1998.
- Member, "BWC Industry Working Group," Belfer Center for Science and International Affairs, Kennedy School of Government, Harvard University, 1998.
- Member, "Biotechnology Research and Industry Working Group", Center for Science and International Affairs, Kennedy School of Government, Harvard University, 1991 - 1993.
- Special Consultant to Tufts University in Biotechnology, 1992 - 1993.
- Managing Partner, Devonshire Biotechnology Group, 1990 - 1992.
- Member Board of Directors, BioTechnica International, Inc., 1981 - 1989.
- Vice President New Business Development, BioTechnica International, Inc., 1986 - 1987.
- Vice Chairman Board of Directors, BioTechnica Diagnostics, 1985 - 1987.
- Vice President Scientific Planning, BioTechnica International, Inc., 1983 - 1986.
- Vice President Scientific Operations, BioTechnica International, Inc., 1981 - 1983.
- Lecturer at the Rank of Associate Professor, Biochemical Sciences, Princeton University, 1979 - 1981.
- Associate Professor, Biochemistry and Molecular Biology, Harvard University, 1975 - 1979.
- Assistant Professor, Biochemistry and Molecular Biology, Harvard University, 1971 - 1975.

Examples of Recent Biotechnology-related Activities

- Developed strategic plan and devised program area for the life-scieicnes effort for a major land-grant university;
- Evaluated for a major investment bank a company's technology, competititors technology, intellectual property and regulatory aspects of products;
- Determined the likely status in the year 2005 of drug discovery and development in a major therapeutic area for a major investment bank;
- Invented, wrote a patent application, carried out a market assessment, and devised a business strategy for a number of agricultural and industrial applications for an array of *in vivo* directed gene mutation methods;
- Carried out a complete analysis of a company's and competitors' intellectual property position;
- Wrote business plans for first and second-stage financing;
- Carried out a formal screening process to decide which of many clinical applications should be pursued for a family of novel small-molecule drugs;
- Conducted a pharmacoeconomic analysis of genetic risk testing; and
- Identified a science/business opportunity from a university's basic research in infectious disease and wrote a strategic plan to exploit the opportunity.
- Helped assemble scientific advisory boards for a startup;
- Wrote first drafts of several patents, some of which were my own inventions;
- Wrote grants that have been awarded; and
- Carried out a mathematical pharmacokinetic analysis of a large-molecule drug-delivery method to justify its development.

Recent Biotechnology-related Presentations:

Speaker "Pharmacoeconomic Consequences of Genetic Risk Assessment for Hereditary Breast Cancer," at conference: New Approaches in Diagnosing and Treating Breast Cancer, sponsored by Cambridge Healthtech Institute, Philadelphia PA, November 1994.

Speaker "Pharmacokinetics and Pharmacoeconomics in Drug Development," at Conference: Pharmacokinetic Analysis sponsored by Cambridge Healthtech Institute, Washington DC, October 1994.

Panel member and speaker, "The Biotechnology Industry" at conference: Technology and Employment, sponsored by MIT, Cambridge MA, January 1994.

Chairperson, organizer, and Keynote Speaker, "Biostrategies" Conference, Presented by the Wang Institute of Boston University. Tyngsboro, Ma., November 1990.

Recent Biological-Weapons-Treaty-Related-Presentations:

Speaker and panel-discussion moderator for a U.S. Congressional Briefing "The Shape of a Compliance Regime for the Biological Weapons Convention," Washington DC, February 1999.

Speaker "Challenge Investigation Voting Procedures for a BWC Compliance Regime: The Effect of Abstentions," at Conference: Association of Politics and the Life Sciences, Boston MA, September 1998.

Speaker "Meeting U.S. Industry Concerns within a Strong BTWC Compliance Regime," at Conference: A Strengthened Biological and Toxin Weapons Convention, Vienna Austria, 1998.

Speaker "Evasion Scenarios and Countermeasures," at Workshop: The Utility of Sampling and Analysis for Compliance Monitoring of the Biological Weapons Convention, Washington DC, October, 1996.

Speaker "FAS and US Industry Recent Discussions," at FORUM: Triggers for Declarations and Inspections/Visits in a BWC Compliance Regime and Incorporation of Export Controls in the Regime, Palais des Nations, Geneva Switzerland, July 1996

Education:

University of California, San Diego. 1966-1971. Ph.D. in Chemistry.
Advisor: Professor Bruno Zimm

Princeton University. 1962-1965. B.A. in Mathematics.

Trenton Junior College Evening Division. 1958-1962.

Outstanding Honors:

Camille and Henry Dreyfus Foundation, Teacher-Scholar Grant, 1975. Single harvard University nominee. At the time, this grant was awarded each year to only six individuals in the U.S.

Research Publications:

Published over 40 research papers and review articles in leading scientific and business journals and awarded two U.S. patents. Ten publications or issued papers on Biological Weapons Control.

Books Published:

Edward J. Sylvester and Lynn C. Klotz, "The Gene Age: Genetic Engineering and the Next Industrial Revolution." Charles Scribner's Sons, New York.

First Edition: 1983, Nominated for Pulitzer Prize by the publisher. Second Edition: 1987.

References

Business:

Dr. Jay George, Assistant Director, Program Technology Development, National Cancer Institute. Bldg. 31, Room 11A03, 31 Center Drive, MSC 2590, Bethesda, MD. 20892-2590. Tel: 301-435-3877. Dr. George was formerly Vice President of Research for Oncor, Inc. and Codon, Inc.

Dr. Ralph Hardy, President, National Agricultural Biotechnology Council. Summer address: 31 Oak Street, Fenelon Falls, Ontario, Canada K0M1N0, summer tel: 705-887-9887, other tel: 607-254-1240. Dr. Hardy was formerly Director of Life Sciences at DuPont, President and Chief Operating Officer at BioTechnica International, and President of the Boyce Thompson Institutute at Cornell University.

Mr. Charles Morris, Devonshire Partners, 100 W. 57th Street Apartment No. 17I, New York NY 10019. Tel: 212-489-9802. Mr. Morris was formerly Group Executive, Chase Manhattan Bank.

Dr. David Bing, Scientific Director of DNA Repository, Genomics Collaborative, 99 Erie Street, Cambridge, MA 02139. Tel: 617-661-2400. Dr. Bing was formerly Vice President, The Center for Blood Research, Inc.

Dr. Sandy Primrose, Chief Operating Officer, Azur Environmental, Ltd., 540-545 Eskdale Road, Winnersh Triangle, Wokingham, Berkshire RGG41 5TU UK. Tel: 011-44-118-927-7000. Dr. Primrose was formerly General Manager of Life Sciences at Amersham International; and Senior Director of Drug Development at Searle.

Academic Science and International Affairs

Professor Jacques R. Fresco, Department of Molecular Biology, Lewis Thomas Laboratory, Princeton University, Princeton NJ 08544: 609-258-3927

Professor Paul Doty, Director Emeritus, Center for Science and International Affairs, John F. Kennedy School of Government and Professor Emeritus, Biochemistry and Molecular Biology, Harvard University, Cambridge MA 02138: 617-495-1404

Dr. Barbara Rosenberg, Chair, Federation of American Scientists Working Goup on Biological Weapons, 307 Massachusetts Avenue NE, Washington DC 20002. Tel: 914-251-6643

Professor Bruno H. Zimm, Department of Chemistry, University of California at San Diego, La Jolla California 92093: 619-534-4416

Professor Thomas M. Roberts, Dana Farber Cancer Institute, 44 Binney Street, Boston MA 02115. Tel: 617-632-3049

Publications:

I. Science publications

Fresco, J.R., Klotz, L.C., and Richards, E.G., (1963). A New Spectroscopic Approach to the Determination of Helical Secondary Structure in Ribonucleic Acids. Cold Spring Harbor Symp. Quant. Biol., 28, 83-90.

Massoulié, J., Blake, R., Klotz, L.C., and Fresco, J.R., (1964). Une Méthode Spectrophotométrique Permettant d'Etudier Séparément les Complexes en Double et Triple Hélice Formés par les Acides Polyriboadénylique et Poly-ribouridylique. C. R. Acad. Sc. Paris, 259, 3104-3107.

Massoulié, J., Guschlbauer, W., Klotz, L.C., and Fresco J.R., (1965). Etude des Complexes Formés par les Acides Poly-adénylique et Polyuridylique. Caractérisation des Complexes par les Spectres Différences. C. R. Acad. Sc. Paris, 260, 1285-1288.

Blake, R.D., Klotz, L.C., and Fresco, J.R., (1968). Temperature Dependence of Kinetics of Complex Formation in Equimolar Mixtures of Polyriboadenylate and Poly-ribouridylate. J. Amer. Chem. Soc., 90, 3556-3562.

Klotz, L.C., (1969). Dependence of Polynucleotide Helix-Coil Transition Theory on the Ring Closure Exponent. Biopolymers, 7, 265-273.

Chapman, R.E., Jr., Klotz, L.C., Thompson, D.S., and Zimm, B.H., (1969). An Instrument for Measuring Retardation Times of Deoxyribonucleic Acid Solutions. Macromolecules, 2, 637-643.

Holdy, K.E., Klotz, L.C., and Wilson, K.R., (1969). Molecular Dynamics of Photodissociation: Quasidiatomic Model for ICN. J. Chem. Phys., 52, 4588-4599.

Klotz, L.C., (1971). Viscosity and Retardation-Time of the DNA in Cell Lysates of B. subtilis and E. coli. Ph.D. Thesis, University of California at San Diego. Prof. Bruno H. Zimm, Thesis advisor.

Klotz, L.C. and Zimm, B.H., (1972). Size of DNA Determined by Viscoelastic Measurements: Results on Bacteriophages, Bacillus subtilis and Escherichia coli. J. Mol. Biol., 72, 779-800.

Klotz, L.C. and Zimm, B.H. (1972). Retardation Times of Deoxyribonucleic Acid Solutions. II. Improvements in Apparatus and Theory. Macromolecules, 5, 471-481.

Klotz, L.C. and Zimm, B.H. (1972). Relaxation Phenomena as a Tool for Studying DNA. Polym. Prep., 13, 25-27.

Kavenoff, R., Klotz L.C., and Zimm, B.H., (1973). On the Nature of Chromosome-sized DNA Molecules. Cold Spring Harbor Symp. Quant. Biol., 38, 1-8.

Roberts, T.M., Tuttle, R.C., Allen, J.R., Loeblich, A.R. III, and Klotz, L.C., (1974). New Genetic and Physiochemical Data on Structure of Dinoflagellate Chromosomes. Nature, 248, 446-447.

Rau, D.C. and Klotz, L.C., (1975). A More Complete Kinetic Theory of DNA Renaturation. J. Chem. Phys., 62, 2354-2365.

Lauer, G.D. and Klotz, L.C., (1975). Determination of the Molecular Weight of Saccharomyces cerevisiae Nuclear DNA. J. Mol. Biol., 95, 309-326.

Allen J.R., Roberts T.M., Loeblich, A.R. III, and Klotz, L.C., (1975). Characterization of the DNA from the Dinoflagellate Crypthecodinium cohnii and Implications forNuclear Organization. Cell, 6, 161.

Muller, W.A., and Klotz, L.C., (1975). Retardation Time Measurements on Replicating Bacillus subtilis Chromosomes: Effect of EDTA Concentration. Biochim. Biophys. Acta, 378, 171-185.

Roberts, T.M., Lauer, G.D., and Klotz, L.C., (1976). Physical Studies on DNA from "Primitive" Eukaryotes. CRC Critical Reviews in Biochem., 3, 359-449.

Lauer, G.D. and Klotz, L.C., (1976). Molecular Weight of Bacteriophage PBS2 DNA. J. Virol., 18, 1163-1164.

Roberts, T.M., Klotz, L.C., and Loeblich, A.R. III, (1977). Characterization of a Blue-green Algal Genome. J. Mol. Biol., 110, 341-361.

Lauer, G.D., Roberts, T.M. and Klotz, L.C., (1977). Determination of the Nuclear DNA Content of Saccharomyces cerevisiae and Implications for the Organization of DNA in Yeast Chromosomes. J. Mol. Biol., 114, 507-526.

Rau, D.C. and Klotz, L.C., (1978). A Unified Theory of Nucleation-Rate-Limited DNA Renaturation Kinetics. Biophys. Chem., 8, 41-51.

Hinnebusch, A.G., Clark, V.E., and Klotz L.C., (1978). Length Dependence in Reassociation Kinetics of Radioactive Tracer DNA. Biochemistry, 17, 1521-1529.

Mitchell, R.M., Loeblich, L.A., Klotz, L.C., and Loeblich, A.R. III, (1979). DNA Organization of Methanobacterium thermoautotrophicum. Science, 204, 1082-1084.

Klotz, L.C., Komar, N., Blanken, R.L., and Mitchell, R.M., (1979). Calculation of Evolutionary Trees from Sequence Data. Proc. Natl. Acad. Sci., U.S.A., 76, 4516-4520.

Hinnebusch, A.G., Klotz, L.C., Immergut, E., and Loeblich, A.R. III, (1980). Deoxyribonucleic Acid Sequence Organization in the Genome of the Dinoflagellate Crypthecodinium cohnii. Biochemistry, 19, 1744-1755.

Klotz, L.C. and Blanken, R.L., (1981). A Practical Method for Calculating Evolutionary Trees from Sequence Data. J. Theor. Biol., 91, 261-272.

Hinnebusch, A.G., Klotz, L.C., Blanken, R.L., and Loeblich, A.R. III, (1981). An Evaluation of the Phylogenetic Position of the Dinoflagellate Crypthecodinium cohnii Based on 5S rRNA Characterization. J. Mol. Evol., 17, 334-347.

Blanken, R.L., Klotz, L.C., and Hinnebusch, A.G., (1982). Computer Comparison of New and Existing Criteria for Constructing Evolutionary Trees from Sequence Data. J. Mol. Evol., 19, 9-19.

Klotz, L.C., (1983). Overproduction of Proteins in Recombinant Organisms. Edited by Venkatasubramanian, K., Constantinides, A., and Vieth, W.R.. Ann. N.Y. Acad. Sci., Biochem. Eng. III, 413, 1-11.

French, C.K., Savitt, E.D., Simon, S.L., Eklund, S.M., Chen, M.C., Klotz L.C., and Vaccaro, K.K. (1986). DNA Probe Detection of Periodontal Pathogens. Oral Microbiol. Immunol., 1, 58-62.

French, C.K., Simon, S.L., Chen, M.C., Eklund, S.M., Klotz, L.C., Vaccaro, K.K., and Savitt, E.D., (1989). DNA Probe Diagnosis of Periodontal Disease. Edited by Swaminathan, B., Prakash, G., and Dekker, M.. Nucleic Acid and Monoclonal Antibody Probes; Applications in Diagnostic Microbiology.

II. Issued patents

U.S. Patent 4,866,167. Issued on September 12, 1989. "Detection of Human Oral Cells by Nucleic Acid Hybridization." Inventors: Michael C. Chen, Pearl M. Chen and Lynn C. Klotz.

U.S. Patent 4,925,785. Issued May 15, 1990. "Nucleic Acid Hybridization Assays." Inventors: Chang-Ning J. Wang and Lynn C. Klotz.

III. Submitted patents and patents in preparation

[illegible]

In preparation:

[illegible]

[illegible]

[illegible]

[illegible]

IV. Business Articles

Klotz, L.C., "Is Genetic Engineering Just Another South Sea Bubble?" Bio/Technology, Jan. 1984.

Klotz, L.C., "Biotech's Future in Bay State." Boston Business Journal, March 26-April 1, 1984.

Kerr, A.P., Klotz, L.C. Morris, C.R. and Schatz, R.W., "A Paradigm for Analyzing Biotechnology Investing and Partnering Opportunities." BioPharm, June 1991.

Kerr, A.P., Klotz, L.C., Morris, C.R. and Schatz, R.W., "An Early Warning Tool for Pharmaceutical Development." BioPharm, Vol. 5, No. 2, February 1992.

Schatz, R.W., Klotz, L.C., Morris, C.R. and Kerr, A.P. (1992). "The Commercial Potential of Human Oligonucleotide Therapies." DR Reports, Decision Resources, Waltham MA.

Klotz, L.C., Schatz, R.W., Morris, C.R. and Kerr, A.P. (1992). "Human Oligonucleotide Therapies: Promises and Pitfalls." Futurescope, Decision Resources, Waltham MA.

Klotz, L.C., Schatz, R.W., Morris, C.R., Kerr, A.P. and Rodgers, R.J. (1992). "Drug Discovery and Development Strategies: A Look at Six Leading Biotechnology Companies." Spectrum Series, Decision Resources, Waltham MA.

Klotz, L.C., Schatz, R.W., Morris, C.R., Kerr, A.P. and Rodgers, R.J. (1993). "Drug Discovery

and Development Strategies: A Look at Six Leading Biotechnology Companies." DR Reports, Decision Resources, Waltham MA.

Branca, A.F. and Klotz, L.C. (1993). "Transdermal Patches: The Forces Driving an Expanding Market", Spectrum Series, Decision Resources, Waltham MA

Klotz, L.C. and Allison M. (1994). "Rational Design of Small Molecule Therapeutics: Assessing Computer-Based Drug Discovery," Therapy Markets and Emerging Technology Series, Decision Resources, Waltham MA.

Sylvester, E.J. and Klotz, L.C. (2000). "Will the 21 st Run on Green or Black Gold?" USA Today, February 1, 2000, p. 15A

V. Biological weapons control publications

Klotz, L.C.--principal author (1995), "Potential for New Approaches to Microorganism Identification," Working Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.

Klotz, L.C. and Rosenberg, B.H. (1996), "Sampling and Analysis of Proprietary Microorganisms while Protecting Confidential Proprietary Information," Working Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.

Ambassador J. Leonard, W. Carpenter, B.H. Rosenberg and L.C. Klotz (1996), "Strengthening the Biological Weapons Convention: the Impact on Confidential Proprietary Information and Property," Working Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.

Klotz, L. C. (1997), "Evasion Scenarios and Countermeasures," in The Utility of Sampling and Analysis for Compliance Monitoring of the Biological Weapons Convention," Monterey Institute for International Studies, Monterey CA, February 1997.

Klotz, L. C. (1997)--principal author "Confidentiality Can Be Protected During Sampling and Analysis in a BWC Compliance Regime," Federation of American Scientists, Working Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.

Klotz, L. C. and Rosenberg, B.H. (1997), "Rapid Resolution of Questions that Might Arise During Nonchallenge Visits," Working Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.

Rosenberg, B.H and Klotz, L. C.--contributor (1997), "Making Random Non-Challenge Visits Friendly," Working Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.

Rosenberg, B. H. and Klotz, L.C. (1998), "Perspectives on BWC Compliance Regime Issues Affecting Industry," Working Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.
L. C. Klotz (1998), "Countermeasures for Possible Evasion Scenarios in Sampling & Analysis," Working Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.

L. C. Klotz (1998), "Meeting U.S. Industry Concerns within a Strong BTWC Compliance Regime," Proceedings of the Conference: A Strengthened Biological and Toxin Weapons Convention, Vienna Austria, 1998.

L.C. Klotz and M. C. Sims (1998), "Challenge Investigation Voting Procedures for a BWC Compliance Regime," The CBW Conventions Bulletin, October 1998.

Klotz, L. C. and Rosenberg, B.H. (1999), "Means for Protecting US Industry Within an Effective Compliance Regime for the Biological Weapons Convention," Working Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.

Klotz, L. C. (1999), "Selected Working Papers from the Ad Hoc Group Negotiating the Biological Weapons Convention Compliance Regime," Working Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.

Klotz, L. C. (1999), "Protection of Confidential Information under a BWC Compliance Regime," U.S. Congressional Briefing Paper, Federation of American Scientists Working Group on Biological and Toxin Weapons Verification.

KLOTZ DEPOSITION EXHIBIT 3

D’S EXHIBIT 517

Lynn C. Klotz, Ph.D.
71 Winslow Avenue
Somerville, MA 02144
Tel: 617-623-6375
Fax: 617-623-6372
E-mail: lynnklotz@compuserve.com

To: Stephen Blewitt
Dana Donovan

Fax: 617-572-1628
Tel: 617-572-9624

Date: August 29, 1998

Included in this fax is the modified proposal, a consulting contract, and for your information, the product development tool from the Harvard course. You will supply the confidentiality agreement.

Jay and I look forward to working with you and carrying out the project.

EXHIBIT
3
KLOTZ
11-16-06
PENGAD 800-631-6989

CONFIDENTIAL
JH 001702

CONSULTING AGREEMENT

This is an agreement, effective as of September 8, 1998, between Lynn C. Klotz and Jay George, individuals residing at 71 Winslow Avenue, Somerville MA 02144 and 12208 McDonald Chapel Drive, Gaithersburg, MD 20878, respectively ("the Consultants") and John Hancock Mutual Life Insurance Company, A Delaware Corporation ("Hancock").

Background

Under the terms set forth below, Hancock desires to retain the services of the Consultants to carry out consulting services as set forth in Exhibit A ("services"), and the Consultants are willing to render such services.

Terms

1. The Consultants agree that for a period of twenty-five days commencing with the effective date of this Agreement, they will, consistent with their other obligations, render to Hancock the services. All such services shall be rendered by the Consultants or by personnel selected by the Consultants who are under confidentiality to the Consultants. The Consultants agree to make all reasonable efforts to carry out the services.

2. Hancock agrees to pay the Consultants for the services a total of $15,390, which shall be payable within two weeks from the date of delivery of the report.

3. The Consultants shall act as independent contractors and not as agents of Hancock and the Consultants shall make no representation as agents of Hancock. The Consultants shall have no authority to bind Hancock or incur other obligations on behalf of Hancock.

4. In the event Hancock discloses information to the Consultants that it considers to be secret or proprietary ("Proprietary Information"), the Consultants agree to maintain the Proprietary Information in confidence and to treat the Proprietary Information with at least the same degree of care and safeguards that they take with their own proprietary information. Proprietary Information shall be used by the Consultants only in connection with services rendered under this Agreement.

Proprietary Information shall not be deemed to include information that:

(a) is in or becomes in the public domain without violation of this Agreement by the Consultants; or

(b) is already in the possession of Consultants, as evidenced by written documents, prior to the disclosure thereof by Hancock; or

© is rightfully received from a third entity having no obligation to Hancock and without

violation of this Agreement by the Consultants.

5. The Consultants warrant that they are under no obligation to any other entity that in any way is in conflict with this Agreement and that they are free to enter into this Agreement.

6. This Agreement may be terminated by Hancock at any time before completion of the services ("early termination"). Notification of termination shall be delivered by certified letter or by a fax to the Consultants. In the event that Hancock terminates this Agreement, the Consultants will be reimbursed by Hancock at the rate of $175 per hour for services already rendered under this Agreement. Reimbursement for expenses for assistants and out-of-pocket expenses will also be reimbursed by Hancock.

7. The secrecy provisions of Section 4 hereof will survive any termination of this Agreement for a period of three years after such termination.

8. This Agreement is not assignable by either party without the consent of the other.

John Hancock Mutual Life Insurance

Company

By:______________________________

Title:____________________________

____

Lynn C. Klotz

____

Jay George

EXHIBIT A

Future Role of Apoptosis and Other Major Technologies In Cancer Drug Discovery and Development

Project scope and goals

The goal of the project is to assess the role and promise of apoptosis and other major science and technology platforms in the discovery and development of drugs and therapies for the treatment and cure of cancer. The assessment will look five years into the future. The science and technologies ("cancer strategies") to be assessed would include:

- Apoptosis (e.g., capsase and kinase inhibitors, receptor binding, etc.);
- Monoclonal antibodies (e.g., cell-targeted anticancer drug delivery);
- Cell-cycle (e.g., telomere targeted drugs);
- Vaccines;
- Oncogenes and tumor suppressors (e.g., p53);
- Cell-surface receptors and signal transduction;
- Angiogenesis;
- Metastasis;
- Gene-targeting (e.g., antisense, gene therapy);
- Combination therapies (e.g., traditional anticancer drugs combined with biotechnology-derived drugs, such as drugs designed to prevent multiple drug resistance); and
- Other science areas as identified during the course of the project.

Each of the above cancer strategies will be assessed and compared to apoptosis cancer strategies from two view points:

- The promise of the science and technology behind the strategies; and
- The prospects for the strategies in a drug development context.

While, all the above cancer strategies will be considered in the assessment, the focus will be on the cancer strategies that show the most promise..

Project outline, tasks and costs

In the following, principal consultants are billed at $175 per hour. Research assistants are billed at $40 per hour. Payment would be due after the first conference call, which will occur within two weeks after the delivery of the final report.

1. Literature and database searches to assess the state and promise of the various cancer strategies, their scope with regard to cancer treatment and cure, and required developments needed to make the science a competitive cancer strategy. *Principal consultants: 4 person-days. Research assistants: 3 person-days. Out-of-pocket expenses (database searches, journal xeroxing, etc.): $600. Total cost: $7,160.*

2. One-hour interviews with three leading academic cancer researchers to learn their views to combine with our analysis. A questionnaire will be prepared in advance and used to help guide the interview. The interviews will not be taped, but will be written up immediately from notes after the interview. Bulleted summaries of the interviews will be prepared. It is expected that the interviews will likely lead to some additional searches and reading. *Principal consultants: 2.5 person-days. Research assistants: 1 person-day. Honorarium to researchers for hour-long interviews: 3 x $250 = $750. Total cost: $4,570.*

3. Prepare a three- to five-page report summarizing the assessment. As a supplement to the report, a bulleted summary of the interviews and xeroxes of key publications with important points highlighted will be provided. *Principal consultants: 2 person-days. Research assistants: 0.5 person-days. Total cost: $2,960.*

4. Deliver by E-mail and/or fax, a copy of the report and the supplement to the report. Two one- hour conference calls to discuss the report. *Principal consultants: 0.5 person-day. Total cost: $700.*

TOTAL PROJECT COST: $15,390

TIME TO COMPLETION: twenty-five days

KLOTZ DEPOSITION EXHIBIT 4

D'S EXHIBIT 518

Lynn C. Klotz, Ph.D.
71 Winslow Avenue
Somerville, MA 02144
Tel: 617-623-6375
Fax: 617-623-6372
E-mail: lynnklotz@compuserve.com

To: Stephen Blewitt
Dana Donovan

Fax: 617-572-1628
Tel: 617-572-9624

Date: September 9, 1998

I have modified the consulting agreement to incorporate your changes and to provide us with a clean copy. I have signed the agreement, and I am forwarding a copy to Jay for him to sign and fax back to you.

Since we have a signed agreement from you, we are off and running on the project.

PENGAD 800-631-6989
EXHIBIT
4
KLOTZ
11-16-06

CONFIDENTIAL
JH 001694

CONSULTING AGREEMENT

This is an agreement, effective as of September 8, 1998, between Lynn C. Klotz and Jay George, individuals residing at 71 Winslow Avenue, Somerville MA 02144 and 12208 McDonald Chapel Drive, Gaithersburg, MD 20878, respectively ("the Consultants") and John Hancock Mutual Life Insurance Company, A Massachusetts Corporation ("Hancock").

Background

Under the terms set forth below, Hancock desires to retain the services of the Consultants to carry out consulting services as set forth in Exhibit A ("services"), and the Consultants are willing to render such services.

Terms

1. The Consultants agree that for a period of twenty-five days commencing with the effective date of this Agreement, they will, consistent with their other obligations, render to Hancock the services. All such services shall be rendered by the Consultants or by personnel selected by the Consultants who are bound by confidentiality agreement with Hancock substantially similar to Confidentiality Agreement between consultants and Hancock dated September 2, 1998 (the "Confidentiality Agreement"). The Consultants agree to make all reasonable efforts to carry out the services.

2. Hancock agrees to pay the Consultants for the services a total of $15,390*, which shall be payable within two weeks from the date of delivery of the report ("Report").

> *Or, in the event of early termination of the project, the amount which represents Consultants incurred-to-date time and services.

3. The Consultants shall act as independent contractors and not as agents of Hancock and the Consultants shall make no representation as agents of Hancock. The Consultants shall have no authority to bind Hancock or incur other obligations on behalf of Hancock.

4. In the event Hancock discloses information to the Consultants that it considers to be secret or proprietary ("Proprietary Information"), the Consultants agree to maintain the Proprietary Information together with the Report in confidence in accordance with the Confidentiality Agreement and to treat the Proprietary Information with at least the same degree of care and safeguards that they take with their own proprietary information. Proprietary Information shall be used by the Consultants only in connection with services rendered under this Agreement.

Proprietary Information shall not be deemed to include information that:

CONFIDENTIAL
JH 001695

(a) is in or becomes in the public domain without violation of this Agreement by the

Consultants; or

(b) is already in the possession of Consultants, as evidenced by written documents, prior to the disclosure thereof by Hancock; or

© is rightfully received from a third entity having no obligation to Hancock and without violation of this Agreement by the Consultants.

5. The Consultants warrant that they are under no obligation to any other entity that in any way is in conflict with this Agreement and that they are free to enter into this Agreement.

6. This Agreement may be terminated by Hancock at any time before completion of the services ("early termination"). Notification of termination shall be delivered by certified letter or by a fax to the Consultants. In the event that Hancock terminates this Agreement, the Consultants will be reimbursed by Hancock at the rate of $175 per hour for services already rendered under this Agreement. Reimbursement for expenses for assistants and out-of-pocket expenses will also be reimbursed by Hancock.

7. The Confidentiality Agreement will survive any termination of this Agreement for a period of three years after such termination.

8. This Agreement is not assignable by either party without the consent of the other.

John Hancock Mutual Life Insurance

Company

By:______________________________

_

Title:______________________________

_

____

Lynn C. Klotz

____

Jay George

EXHIBIT A

Future Role of Apoptosis and Other Major Technologies In Cancer Drug Discovery and Development

Project scope and goals

The goal of the project is to assess the role and promise of apoptosis and other major science and technology platforms in the discovery and development of drugs and therapies for the treatment and cure of cancer. The assessment will look five years into the future. The science and technologies ("cancer strategies") to be assessed would include:

- Apoptosis (e.g., capsase and kinase inhibitors, receptor binding, etc.);
- Monoclonal antibodies (e.g., cell-targeted anticancer drug delivery);
- Cell-cycle (e.g., telomere targeted drugs);
- Vaccines;
- Oncogenes and tumor suppressors (e.g., p53);
- Cell-surface receptors and signal transduction;
- Angiogenesis;
- Metastasis;
- Gene-targeting (e.g., antisense, gene therapy);
- Combination therapies (e.g., traditional anticancer drugs combined with biotechnology-derived drugs, such as drugs designed to prevent multiple drug resistance); and
- Other science areas as identified during the course of the project.

Each of the above cancer strategies will be assessed and compared to apoptosis cancer strategies from two view points:

- The promise of the science and technology behind the strategies; and
- The prospects for the strategies in a drug development context.

While, all the above cancer strategies will be considered in the assessment, the focus will be on the cancer strategies that show the most promise..

Project outline, tasks and costs

In the following, principal consultants are billed at $175 per hour. Research assistants are billed at $40 per hour. Payment would be due after the first conference call, which will occur within two weeks after the delivery of the final report.

1. Literature and database searches to assess the state and promise of the various cancer strategies, their scope with regard to cancer treatment and cure, and required developments needed to make the science a competitive cancer strategy. *Principal consultants: 4 person-days. Research assistants: 3 person-days. Out-of-pocket expenses (database searches, journal xeroxing, etc.): $600. Total cost: $7,160.*

2. One-hour interviews with three leading academic cancer researchers to learn their views to combine with our analysis. A questionnaire will be prepared in advance and used to help guide the interview. The interviews will not be taped, but will be written up immediately from notes after the interview. Bulleted summaries of the interviews will be prepared. It is expected that the interviews will likely lead to some additional searches and reading. *Principal consultants: 2.5 person-days. Research assistants: 1 person-day. Honorarium to researchers for hour-long interviews: 3 x $250 = $750. Total cost: $4,570.*

3. Prepare a three- to five-page report summarizing the assessment. As a supplement to the report, a bulleted summary of the interviews and xeroxes of key publications with important points highlighted will be provided. *Principal consultants: 2 person-days. Research assistants: 0.5 person-days. Total cost: $2,960.*

4. Deliver by E-mail and/or fax, a copy of the report and the supplement to the report. Two one- hour conference calls to discuss the report. *Principal consultants: 0.5 person-day. Total cost: $700.*

TOTAL PROJECT COST: $15,390

TIME TO COMPLETION: twenty-five days

KLOTZ DEPOSITION EXHIBIT 6

D'S EXHIBIT 802

JOHN HANCOCK MUTUAL LIFE INSURANCE COMPANY
Bond & Corporate Finance Group
March 24, 1999

Private

Purchase Recommendation
JH Pension $5.0 million

Summary
Idun Pharmaceuticals, Inc.
La Jolla, CA

We are recommending the purchase of 1,428,572 shares of Series F Convertible Preferred Stock of Idun Pharmaceuticals, Inc. ("Idun" or the "Company") for $5 million. The Preferred Stock will be convertible into approximately 3.7% of the fully diluted common stock of the Company. Proceeds from the Preferred Stock, together with $5 million of additional Preferred Stock, will be used for working capital and general corporate purposes, including funding continued research and development, technology in-licensing, clinical trials, and related capital expenditures.

Founded in 1993, Idun is a biopharmaceutical company focused on the design and development of small molecule therapeutics targeting the biochemical pathways that control apoptosis, or programmed cell death. Inappropriate regulation of apoptosis contributes to a wide array of diseases including neurodegenerative diseases such as ALS and Parkinson's, cancer, and stroke. Idun has previously received $7 million in venture capital financing and has received over $35 million in capital from Novartis and Abbott, its corporate partners in the field of central nervous system drugs and cancer drugs, respectively.

In addition to the development projects that Idun is pursuing with its corporate partners, the Company is also developing proprietary compounds that regulate apoptosis in diseases such as liver failure, inflammation, and cardiovascular disease. Idun believes that it is approximately one year away from entering Phase I clinical trials with a compound for acute alcoholic hepatitis. The Company intends to develop compounds for clinical trials for other diseases in subsequent years.

Our recommendation is based upon the strength of Idun's management and scientific team, the broad spectrum of diseases that Idun's research applies to, and the potential for substantial equity returns.

Report Authors:
Anthony C. Urick, Second Vice President
Stephen J. Blewitt, Senior Investment Officer
D. Dana Donovan, Senior Investment Officer

(t:\industrl\sjb\yellows\idun-y01.doc)

PENGAD 800-631-6989 EXHIBIT 6 KLOTZ 11-16-06

HIGHLY CONFIDENTIAL
JHII 012355

JOHN HANCOCK MUTUAL LIFE INSURANCE COMPANY
Bond & Corporate Finance Group
March 24, 1999

Private

Purchase Recommendation
JH Pension $5.0 million

ISSUER:	**Idun Pharmaceuticals, Inc.**
ISSUE:	1,428,572 shares of Series F Convertible Preferred Stock
RATINGS:	JH: CCC
BROKER:	Direct
CONVERSION PRICE:	$3.50 per share.
CONVERSION:	*The Preferred Stock may be converted at any time, at the Investor's option, into shares of the Company's Common Stock; par value $0.01 per share. The Preferred Stock will be convertible on a share for share basis into Common Stock, subject to adjustment pursuant to anti-dilution provisions. The Preferred Stock shall be automatically converted into Common Stock (I) in the event that a majority of the holders of the outstanding Preferred Stock consent to such conversion, or (ii) upon the closing of a firmly underwritten public offering with a public offering price of not less than [$3.50] per share and [$7,500,000] in aggregate proceeds.*
DIVIDENDS:	The holders of the Preferred Stock will be entitled to receive non-cumulative dividends prior to any payment of any cash dividend, at a rate of $.175 per share, or, if greater, an amount equal to that paid on any other outstanding shares of the Company's capital stock.
LIQUIDATION PREFERRENCE:	*In the event of any liquidation, dissolution or winding up of the Company, the holders of Preferred Stock shall be entitled to receive the greater of (I) $3.50 per share, plus accrued and unpaid dividends, if any, or (ii) the amount the Investor would be entitled to receive if the Investor had converted such shares of the Preferred Stock into Common Stock immediately prior to the effectiveness of the event giving rise to such payment, out of the assets of the Company.*
MANDATORY REDEMPTION:	*Redemption is mandatory upon the occurrence of a liquidity event (e.g., merger, redemption of other Preferred Stock or sale of assets). In the absence of a liquidity event, redemption will begin on the fifth anniversary of investment with eight quarterly installments, including accrued and unpaid dividends, if any.*
SIC CODE:	8000 - Health Services
PARTICIPANTS:	John Hancock $5.0 million Other Investors: $5.0 million
HANCOCK PARTICIPANTS:	Listed above

HIGHLY CONFIDENTIAL
JHII 012356

USE OF PROCEEDS:	The net proceeds from the convertible preferred stock will be used for working capital and general corporate purposes, including funding continued research and development, technology in-licensing, clinical trials, and related capital expenditures.
STATE OF INC.:	Delaware
CIRCLE DATE:	February 26, 1999
TAKEDOWN DATE:	Upon completion of documentation
CALL:	Non-callable
HANCOCK HOLDINGS:	None
RELATED HOLDINGS:	None
FINANCIAL COVENANTS:	None
ANTI-DILUTION PROVISIONS:	*The Conversion Price of the Preferred Stock will be subject to proportional adjustment for stock splits, stock dividends, recapitalizations and the like.*
REGISTRATION RIGHTS:	*Customary for transactions of this type*
ANALYST:	Stephen J. Blewitt, Senior Investment Officer D. Dana Donovan, Senior Investment Officer
HOUSE COUNSEL:	Amy Weed, Esq.
SPECIAL COUNSEL:	Choate, Hall & Stewart

Report Authors:
Anthony C. Urick, Second Vice President
Stephen J. Blewitt, Senior Investment Officer
D. Dana Donovan, Senior Investment Officer
(t:\industrl\sjb\yellows\idun-y01.doc)

IDUN PHARMACEUTICALS, INC.

Idun Pharmaceuticals, Inc. ("Idun" or the "Company") is a biopharmaceutical company focused on the design and development of small molecule therapeutics targeting the biochemical pathways that control apoptosis, or programmed cell death. Inappropriate regulation of cell death, or apoptosis, contributes to a wide array of diseases including neurodegenerative diseases (ALS, Parkinson's), cancer, and ischemic disorders (stroke). Idun's patented core technologies focus on the pathways that regulate cell death. The Company is developing small molecule drugs that specifically control the function of key proteins involved in the process of cell death: the caspase protease family of cell death effectors and the cell death modulators of the Bcl-2 family.

> *Apoptosis*. Throughout the course of normal development and aging, certain cells and cell types are programmed to die in a controlled manner, a process known as apoptosis. This process is essential for the correct formation of the organs and complex systems of the body and is different than *necrosis* which occurs when a cell is severely injured and internal organelles swell and rupture. Cells that die by apoptosis shrink and are rapidly eaten by neighboring cells before there is any leakage of their contents. In the adult, dysfunction of the mechanisms that control apoptosis can lead to a variety of diseases. Excessive apoptosis results in the unwanted loss of healthy cells resulting in degenerative diseases. Insufficient apoptosis can lead to the uncontrolled cell accumulation most dramatically evident in cancer.
>
> *Bcl-2*. Bcl-2 is a family of genes that can inhibit apoptosis or enhance apoptosis. Elevated Bcl-2 levels may occur in as many as 50% of all cancers, including 20-40% of prostate, 60-80% of breast, 50-70% of colorectal and 20-40% of certain lung cancers
>
> *Caspases*. Caspases are a family of proteases (enzymes that cleave proteins essential to cellular functioning) responsible for carrying out the cell death process. In a living cell, these proteases are kept inactive by Bcl-2 proteins on the mitochondrial cell surface. When a cell is exposed to cell death signals such as ischemia, chemotherapy or radiation, Bcl-2 function is blocked and caspase activators initiate the cell death cascade.
>
> *Caspase Activators*. Caspases are converted from their inactive form to active proteases with the help of caspase activator proteins. One such caspase activator is Apaf-1.

Idun is pursuing drug discovery programs in three areas: degenerative diseases of the central nervous system ("CNS"), cancer, and organ damage outside the CNS. With its CNS partner, Novartis, Idun is pursuing caspase protease inhibitors for the treatment of acute stroke, Parkinson's Disease and Amyotrophic Lateral Sclerosis ("ALS"). With its cancer partner, Abbott, Idun is pursuing small molecule antagonists of anti-apoptotic proteins, including those of the Bcl-2 family. Idun also has an unpartnered program focused on the development of caspase protease inhibitors for treating acute organ damage.

Idun was founded in 1993 and has received $7 million of venture capital financing from Accel Partners, Venrock Associates, Arch Development Corp. (University of Chicago), Avalon Ventures and Delphi BioVentures. The Company has also received $33 million of Preferred Stock investments from Novartis and Abbott, and $20 million of research and development payments from Novartis.

HIGHLY CONFIDENTIAL
JHII 012358

NOVARTIS AGREEMENT

In 1995, Idun established a major research and development collaboration with Novartis, Ltd. Under this four-year agreement, the companies formed an exclusive collaboration to develop drugs to control apoptosis in Central Nervous System ("CNS") diseases. As part of the agreement, Novartis purchased $6 million of preferred stock in Idun (at $2/share), provided Idun with a $12 million credit facility that can be converted into equity prior to August 2006, and funds $6 million per year in research and development expenses. Future compensation to Idun will include milestone payments and royalties on any products that are approved and marketed by Novartis.

Currently, Idun and Novartis have discovered several series of caspase inhibitors that inhibit nerve cell apoptosis and are being optimized for potency and bioavailability. Idun believes the first therapeutic application of its caspase protease inhibitors in the CNS will be in acute administration following a stroke. Experiments on animal models of stroke suggest that as much as 50% of the resulting cell death is apoptotic. Recent studies have demonstrated that caspases become activated in ischemic neurons and that caspase inhibitors can decrease the damage resulting from cerebral ischemia. Novartis plans to start clinical trials in 1999 with one of Idun's caspase inhibitors.

Future therapeutic applications from the Idun/Novartis collaboration may include Parkinson's disease, ALS, and alzheimer disease.

ABBOTT AGREEMENTS

In December 1998, Idun established an exclusive collaboration with Abbott Laboratories to discover and develop small molecule cancer therapeutics that target the apoptosis pathway. These targets include the anti-apoptosis Bcl-2 family of proteins and the pro-apoptotic caspase activator, Apaf-1. In this collaboration, Idun is primarily responsible for developing molecular assays against targets in the core of the apoptosis pathway. These assays will be used by Abbott for high-through-put screening of compound libraries and compound analysis. Abbott will ultimately be responsible for the clinical development and marketing of any drugs that come out of this collaboration. In addition to Abbott's support of research and early development activities ($15 million over three years), Abbott purchased $15 million of preferred stock of Idun at $3.50/share. Future compensation to Idun will include milestone payments and royalties on any products that are approved and marketed by Abbott.

Cancer can be considered a consequence of failure of abnormal cells to undergo apoptosis. Normal cells are dependent both on the presence of survival signals and on the absence of signals generated by sensors that monitor cellular damage. However, cancer cells survive without their tissue-specific survival signals and in the presence of cellular abnormalities that normally would lead to the induction of apoptosis. Cancer cells often accomplish this by up regulation of anti-apoptotic proteins like Bcl-2 or Bcl-x, thereby raising the "apoptotic threshold." Abnormal Bcl-2 expression is found in as many as 80% of breast, small cell lung, and prostate cancers and in a significant percentage of other cancers such as non Hodgkin's lymphoma and colorectal cancer.

IDUN'S PROPRIETARY HEPATIC DISEASE PROGRAM

Cells within the liver can undergo apoptosis due to viral infection, ischemia/reperfusion and hepatotoxic agents. Apoptosis has been observed in biopsies from patients with acute alcoholic hepatitis as well as in animal models of the disease. Alcoholic liver disease is a major health problem in the US, affecting approximately 2 million people. Acute alcoholic hepatitis presents in about 85,000 patients a year in the United States. Effective therapy is not available and current therapy is only supportive, with a significant mortality rate (10-40%). Idun believes that caspase inhibitors that prevent hepatic apoptosis triggered by a variety of stimuli may be useful in treating acute liver failure and liver failure in the setting of chronic liver disease. The Company has chosen alcoholic hepatitis as its first lead clinical indication and has demonstrated in animal models that administration of caspase inhibitors can inhibit the induction of ALT activity detected in the blood. ALT (alanine aminotransferase) is a liver enzyme, high blood levels of which are indicative of liver damage. Significantly improved survival (decrease in mortality) of treated animals has also been demonstrated following administration of Idun's caspase inhibitors.

Based on performance in the relevant preclinical efficacy models, one of Idun's proprietary small molecule caspase inhibitors has been selected as a lead compound, which is currently undergoing formulation, stability studies, toxicology testing, and GMP manufacturing. Idun expects to file an Investigational New Drug (IND) application in early 2000 and start a Phase I clinical trial in humans in acute alcoholic hepatitis shortly thereafter.

Strengths

- **Management and Scientific Team.** Abbott Laboratories and John Hancock's independent science consultants (Allan B. Haberman, Ph.D. and Lynn Klotz, Ph.D.) have each indicated that Idun's Scientific Advisory Board ("SAB") are worldwide leaders in the field of apoptosis research and are networked better than any other research group in their field. For example, two of the Company's Board members, Drs. Horvitz and Korsmeyer, recently received General Motors Cancer Research Foundation awards recognizing their individual achievements in cancer research. Dr. Horvitz's award relates to his identification of a set of genes that comprise the programmed cell death pathway, demonstrating that apoptosis is an active biological process that is genetically determined. Dr. Korsmeyer's award relates to the discovery of a gene (Bcl-2) that suppresses apoptosis.

- **Strong Patent Portfolio.** The strength of the Company's Scientific Advisory Board has enabled the Company to establish a strong portfolio of proprietary technology encompassing 34 patent families including 37 issued patents related to the cell death process. Idun has exclusive license to the patented sequence of the human proto-oncogene bcl-2, as well as related genes including bax, bcl-x, bad and mcl-1. The Company controls patent applications covering key cell death proteases including caspases 1, 3, 6, 7, 8, 9 10, and 13. Idun has licensing agreements covering intellectual property from Dartmouth, Thomas Jefferson University, The Burnham Institute, MIT, the University of Michigan, Washington University and Arch Development Corporation.

- **Reasonable Valuation/Potential for Strong Returns.** Post-closing, Idun's equity value will be approximately $133 million (based on 38 million shares at $3.50/share). The Company's technology value (equity value minus cash) will be approximately $93 million. Based on our analysis of public company valuations and valuations of private companies at pre-IPO financing, $3.50/share appears to be a reasonable price for Idun. The technology value of companies that have recently received private equity and are similar to Idun (cancer related or signal transduction related), such as Mitotix, Signal, Ilex, Onyx and Sugen, were approximately $70 - $90 million before the recent sector-wide increase in values. Valuations for similar public companies, such as OSI, Isis, Imclone, Entremed, Sugen, Ilex, and Cell Pathways, are approximately $200 – 300 million. This range of public company valuations reflect particular corporate collaborations and the development stage of products.

We believe that Idun's collaborations with Novartis and Abbott and the strong probability that it will have several compounds in clinical trials in the next few years will likely provide an IPO value of at least $300 million – which will result in an IRR of approximately 30% over three years.

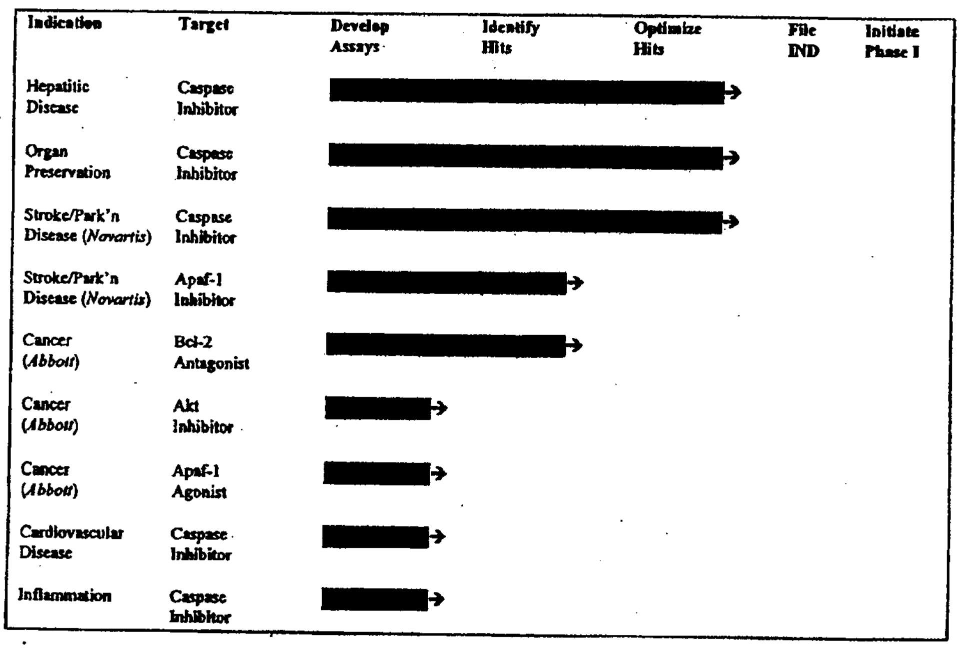
- **Apoptosis is Broad Platform.** Many serious diseases result from the improper regulation of apoptosis resulting in either too much or too little apoptosis. Idun has a number of research and development programs at various stages, ranging from early discovery to IND filing planned for 1999. As described more fully above, these programs involve a wide variety of diseases, including cancer, CNS, liver disease, cardiovascular disease and inflammation.

Apoptosis has been observed in biopsies from patients with acute alcoholic hepatitis as well as in animal models of the disease. Recent biochemical, morphological and pharmacological observations indicate that

apoptosis accounts for a significant portion of the cell death that occurs following cerebral injury or ischemia (decreased blood flow). Bcl-2 expression has been shown to be upregulated in clinical models of follicular lymphomas, prostate cancer, breast cancer and other cancers. *In vitro* studies in numerous cancer cell lines have demonstrated that overexpression of Bcl-2 leads to multi-drug resistance. Studies in animal models of myocardial infarction (heart attack) suggest that apoptosis may contribute substantially to cell death. Studies have shown that inactivation of caspase 1 decreases production of certain cytokines and is protective in animal models of arthritis and septic shock.

John Hancock commissioned two consultants to review the field of anti-cancer therapies and project the importance of various cancer therapies in five years. Dr. Allan Haberman, a principal of the Biopharmaceutical Consortium, has indicated that apoptosis is one of the two most significant areas of research in the treatment of all cancers (the other being angiogenesis) while research into cancer vaccines and anti-metastatic therapies are significant but more limited. Dr. Lynn Klotz of Harvard University and Dr. Jay George, Assistant Director – National Cancer Institute, have concluded that if small molecule apoptosis-inducing drugs with reasonable pharmacological properties can be discovered and developed, those drugs combined with traditional anticancer drugs would find wide use. Drs. Klotz's and George's conclusions were based on their independent research and personal interviews with three prominent oncologists.

Idun's Product Pipeline



HIGHLY CONFIDENTIAL
JHII 012361

Risks and Mitigating Factors

- **Early stage of product development.** Although Idun's corporate partnerships with Novartis and Abbott as well as its own proprietary drug discovery efforts provide several avenues for potential success, it is possible that Idun's research in apoptosis does not lead to the discovery of any meaningful drug compounds. In addition, the development and commercial use of the Company's products are regulated as drugs by the FDA and comparable foreign regulatory agencies. The regulatory approval process for new drugs and drug delivery systems, including required preclinical studies and clinical trials, is lengthy and expensive. There can be no assurance that the necessary FDA clearances and subsequent approvals of the Company's products will be obtained in a timely manner, if at all. The failure by Idun or its corporate partners to develop a commercially successful drug would likely result in a loss of significant value to Idun's shareholders.

We believe that this risk is mitigated by the breadth of Idun's technology platform and the strength of the Company's corporate partners.

- **Need for additional capital.** The Company expects that its existing capital resources, together with the estimated net proceeds from this offering, will enable the Company to maintain its current and planned operations for the next 30 months. Idun will need to raise substantial additional funds through additional financings including public or private equity offerings and collaborative research and development arrangements with corporate partners. We believe that through the results of its own proprietary research programs, its collaborations with Novartis and Abbott, or products that it may in-license, Idun will have one or more products in clinical trials during the next three years. At that stage, Idun will be able to raise substantial capital in an initial public offering, merger, or other corporate financing, that will allow the Company to successfully complete its trials and bring a product to market.

- **Idun faces significant competition.** Competition in the research and development of therapeutics in the apoptosis field is intense and expected to increase. To date, there have been no FDA approvals of therapeutics in this field. The Company believes that other medical and pharmaceutical companies are engaged in research and development in the apoptosis field (e.g., Merck, Vertex and others). In addition, other technologies or products may be developed that have an entirely different approach or means of accomplishing the enhancement of apoptosis therapeutics that would render the Company's technology and products uncompetitive.

In the "core" of the apoptosis pathway, Idun has licensed extensively to create a formidable patent portfolio. In its two target focuses, Bcl-2 family and caspases, Idun has seven issued patents covering eight genes. These patents do not guarantee Idun freedom to operate in the future in all of its activities, but they do provide two important things: 1) a strong patent position to negotiate with competitors that may have related or overlapping intellectual property; and 2) an incentive for large pharmaceutical companies (some of which are competitors today) to invest resources and contribute their expertise (through partnership) to the development of Idun's drug targets. To attract partners, Idun has supplemented its patents with additional intellectual property or know-how, including the recognized thought leaders in the apoptosis field (Scientific Advisory Board and Consultants) and high quality, peer-reviewed basic research in apoptosis biology. Both of these activities place Idun in a strong competitive position regarding identification and optimization of compounds that interact with the key apoptosis regulatory molecules.

HIGHLY CONFIDENTIAL
JHII 012362

PRINCIPAL STOCKHOLDERS

	Prior to Offering Number of Shares	After Offering Number of Shares	Percentage Owned (fully diluted)
PREFERRED STOCKHOLDERS			
Novartis	5,981,366	5,981,366	15.7%
Abbott	4,285,714	4,285,714	11.2%
Venture Capital Firms	11,324,272	12,752,844	33.4%
John Hancock	0	1,428,572	3.7%
Others	2,341,540	2,341,540	6.1%
	23,932,892	26,790,035	70.2%
COMMON STOCKHOLDERS	7,546,268	7,546,268	19.8%
Issued Options/Warrants	3,801,084	3,801,084	10.0%
TOTAL SHARES (FULLY DILUTED)	35,280,244	38,137,387	100.0%

BOARD OF DIRECTORS

Costa G. Sevastopoulos, Ph.D.	Chairman, President and CEO of Ixsys, Inc.
Anthony B. Evnin, Ph.D.	General Partner of Venrock Associates
John C. Reed, M.D., Ph.D.	Scientific Director of the Burnham Institute
Paul H. Klingenstein.	Klingenstein Management
Steven J. Mento, Ph.D.	President and CEO of Idun Pharmaceuticals, Inc.
Stanley T Crooke, M.D., Ph.D.	Chairman and CEO of Isis Pharmaceuticals

SCIENTIFIC ADVISORY BOARD

John C. Chabala, Ph.D.	President and Chief Scientific Officer of Pharmacopeia, Inc.
Carlo M. Croce, M.D.	Director, Kimmel Cancer Institute (Thomas Jefferson University)
H. Robert Horvitz, Ph.D.	Professor of Biology at MIT
Stanley J. Korsmeyer, M.D.	Director of Molecular Oncology at the Dana-Farber Cancer Institute
Martin Raff, M.D.	Professor of Molecular Neurobiology at University of College London
John C. Reed, M.D., Ph.D.	Scientific Director of The Burnham Institute
Craig Thompson, M.D.	Professor of Medicine at University of Chicago

MANAGEMENT

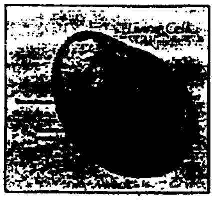
Steven J. Mento, Ph.D. President, CEO and Director since 1997. Prior to joining Idun, Dr. Mento was President of Chiron Viagene and Vice President of Chiron from 1992 to 1997. Dr. Mento also held various positions with American Cyanamid Corporation from 1982 to 1992, including Director of Viral Vaccine Research and Development at Lederle-Praxis Biologicals.

Kevin J. Tomaselli, Ph.D. Vice President, Science and Technology. Prior to founding Idun, Dr. Tomaselli was formerly a Senior Scientist at Athena Neurosciences, Inc. Dr. Tomaselli received his B.S. degree in Biology from Tufts University and his Ph.D. in Neuroscience from the University of California, San Francisco.

M.J. Winship, M.D. Vice President of Product Development. Dr. Winship joined Idun in 1998. Previously, he held director positions at Hoechst Mario Roussel and was Medical Director for Clinical Research at IMMUNOMEDICS, Inc. Dr. Winship received his B.S. degree in Medicine and his M.D. from Northwestern University.

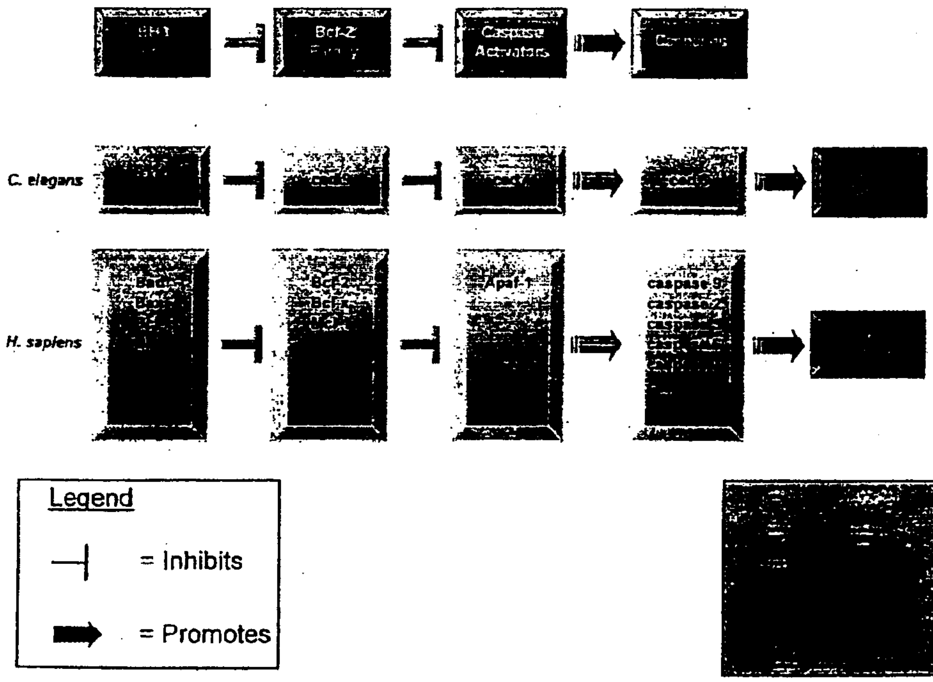
HIGHLY CONFIDENTIAL
JHII 012363

Scientific Overview



Apoptosis is a genetically controlled form of cell suicide. Apoptosis, or programmed cell death, is important for embryonic development as well as the maintenance of adult tissues and organs. Insufficient or excessive apoptosis contributes to a number of human diseases. The genes and proteins that comprise the apoptosis pathway were initially identified genetically in model organisms, for example, in the roundworm *C. elegans*, and are recapitulated in human cells (Figure 1).

Figure 1. The Apoptosis Pathway



Idun Pharmaceuticals, Inc.

Balance Sheets

	December 31 1998	1997
Assets		
Current assets:		
Cash and cash equivalents	$25,436,051	$ 2,612,040
Short-term investments, available-for-sale	4,515,535	11,548,883
Interest receivable	219,313	431,184
Other current assets, net	130,519	160,213
Total current assets	30,301,418	14,752,320
Cash-restricted	349,307	508,085
Property and equipment, net	2,366,878	1,945,106
Other assets	56,721	5,981
	$33,074,324	$17,211,492
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 255,087	$ 155,596
Accrued expenses	604,325	563,196
Current portion of capital lease obligations	745,182	685,362
	1,604,594	1,404,154
Deferred revenue from related party	7,500,000	1,500,000
Capital lease obligations, less current portion	1,122,758	924,717
Note payable to related party, including accrued interest	13,675,233	12,955,233
Commitments		
Stockholders' equity:		
Preferred stock, $.001 par value; 28,291,667 shares authorized, issuable in series:		
Series A convertible, 1,225,000 shares authorized, 745,000 shares issued and outstanding, liquidation preference of $74,500	745	745
Series B convertible, 13,500,000 shares authorized, 12,862,315 shares issued and outstanding, liquidation preference of $7,099,998	12,862	12,862
Series C convertible, 9,200,000 shares authorized, 3,043,097 shares issued and outstanding, liquidation preference of $6,086,194	3,043	3,043
Series D convertible, 66,667 shares authorized, 15,400 shares issued and outstanding, liquidation preference of $46,200	15	-
Series E convertible, 4,300,000 shares authorized, 4,285,715 shares issued and outstanding, liquidation preference of $15,000,003	4,286	-
Common stock, $.001 par value; 75,000,000 shares authorized, 7,546,268 and 5,575,092 shares issued and outstanding at December 31, 1998 and 1997, respectively	7,546	5,575
Additional paid-in capital	28,455,169	13,238,096
Note receivable from officer	-	(37,500)
Unrealized gain on short-term investments	4,342	7,378
Accumulated deficit	(19,316,269)	(12,802,811)
Total stockholders' equity	9,171,739	427,388
	$33,074,324	$17,211,492

HIGHLY CONFIDENTIAL
JHII 012365

Idun Pharmaceuticals, Inc.

Statements of Operations

	Years ended December 31	
	1998	1997
Revenue under collaborative research agreements with related parties	$ 6,417,781	$ 6,187,501
Costs and expenses:		
Research and development	10,334,215	7,987,485
General and administrative	2,422,348	2,168,790
Total costs and expenses	12,756,563	10,156,275
Loss from operations	(6,338,782)	(3,968,774)
Interest income	691,068	918,995
Interest expense	(865,744)	(891,401)
Net loss	(6,513,458)	(3,941,180)
Unrealized gain (loss) on short-term investments	(3,036)	7,378
Comprehensive net loss	$(6,516,494)	$(3,933,802)

HIGHLY CONFIDENTIAL
JHII 012366

Idun Pharmaceuticals, Inc.

Statements of Cash Flows

	Years ended December 31 1998	1997
Operating activities		
Net loss	$(6,513,458)	$(3,941,180)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	728,125	572,343
Loss on disposal of property and equipment	3,877	–
Forgiveness of note receivable from officer	37,500	37,500
Changes in assets and liabilities:		
Cash-restricted	158,778	126,915
Other current assets	240,569	(195,478)
Other assets	(50,740)	21,999
Accounts payable	126,685	(15,524)
Deferred revenue	(1,500,000)	1,312,499
Accrued expenses	807,329	851,916
Net cash used in operating activities	(5,961,335)	(1,229,010)
Investing activities		
Purchases of marketable securities	(5,548,777)	(16,114,045)
Proceeds from sales/maturities of marketable securities	12,579,089	8,450,000
Purchases of property and equipment	(1,154,882)	(45,638)
Proceeds on disposal of property and equipment	2,104	–
Net cash provided by (used in) investing activities	5,877,534	(7,709,683)
Financing activities		
Proceeds from note payable to related party *(Note 2)*	7,500,000	–
Proceeds from capital lease obligations	990,224	–
Payments on capital lease obligations	(759,557)	(598,625)
Proceeds from issuance of Series E convertible preferred stock, net	14,960,003	–
Proceeds from issuance of common stock, net	217,142	38,440
Net cash provided by (used in) financing activities	22,907,812	(560,185)
Net increase (decrease) in cash and cash equivalents	22,824,011	(9,498,878)
Cash and cash equivalents at beginning of year	2,612,040	12,110,918
Cash and cash equivalents at end of year	$25,436,051	$ 2,612,040
Supplemental schedule of noncash activities:		
Property and equipment acquired under capital lease obligations	$ –	$ 371,407
Conversion of accounts payable to capital lease obligations	$ 27,194	$ 145,755
Issuance of Series D convertible preferred stock	$ 46,200	$ –
Supplemental disclosure of cash flow information:		
Interest paid	$ 145,744	$ 171,401

HIGHLY CONFIDENTIAL
JHII 012367

KLOTZ DEPOSITION EXHIBIT 7

D'S EXHIBIT 550

From: Lynn C. Klotz [LynnKlotz@compuserve.com]
Sent: Tuesday, June 20, 2000 6:46 PM
To: Blewitt, Stephen
Subject: Preliminary Abbott basket analysis

It took me less time than I thought to consolidate my notes, so here it is in the attachment. I will not do any more work, until we agree on next steps. I am a little under two days work so far.

-- Lynn

EXHIBIT
PENGAD 800-631-6989
7
KLOTZ
11-16-06

Confidential Property of John Hancock
(prepared by Lynn C. Klotz, PhD)

Preliminary Analysis of Abbott Drug Basket

file: abbott-bask

General Thoughts, Ideas and Questions

The basket is really two baskets

Some of the drugs in the basket are well along in clinical trials and represent new but more traditional approaches to diseases. In contrast, the remaining drugs are cytostatic cancer agents for cancer, and since this is a new untried strategy for everyone, it is high risk. The risk is compounded by the fact that most are in discovery, not in clinical trials.

In our analysis, we should perhaps treat the basket as two, and come up with independent courses of action for each. The traditional drugs in the basket cover a wide range of diseases and thus reduce the risk of competitor's drugs totally shutting Abbott out.

Some thoughts on cytostatic drugs

There is a general clinical trials issue for cytostatic drugs: Many will enter trials in combination with conventional cytotoxic drugs and effective combinations will have to be determined empirically. Intermediate and surrogate measures of biological response will have to be developed. Regulatory agencies are grappling with the same issues.

The idea of using cytostatic drugs in combination with traditional drugs is however enormously appealing.

Do cytostatic agents reflect Abbott's major cutting-edge cancer strategy? If not, why are they being offered to Hancock?

Precisely what is Hancock buying?

In the areas where Abbott is still in discovery and doesn't have specific drug candidates will Hancock be buying royalty rights for all compounds, the first to enter clinical trials or the first to enter the marketplace. Rights to the first to enter the marketplace is greatly preferred, since it eliminates the risk that the drug will make it through trials. This is one way to deal with the cytostatic area where the candidates are not yet in clinical trials.

For some compounds, Abbott is conducting clinical trials for one indication, but they state that the compound has shown promise for other indications (off label or not) and diseases. It is

preferable that Hancock has royalty rights for the compound itself– that is all indications and diseases, rather than the first indication for which it is being tested in trials. .

How do we value the technical aspects of the drug basket and competitive drugs?

First, we might search the business press and MedLine to validate Abbott's claims and analysis for each drug in the basket. Then, for some (many?) basket drugs we should seek the opinion of one to two experts. Literature searching one basket drug is likely a four to five hour task, and may be necessary preparation to prime us with goodquestions for the experts. We should not need more than two hours of an expert's time. From the point of view of due diligence, experts should be retained for most of the drugs.

How do we value sales of the drug basket?

Estimating actual sales of drugs in the basket is difficult, but is key for deciding on the amount of investment and royalty rate. Along with clinical trials, success risk it is the other main source of risk, assuming Abbott doesn't just disappear. Abbott's sales estimates are likely all high, because they would need to be optimistic to sell the drugs/programs internally. A few ideas for schemes for estimating sales are presented below:

1) In this scheme, determine the dollar sales for the top five (ten or twenty?) drugs in each therapeutic area (disease targets), and the average sales of all drugs in that disease area. This data is likely available for many of the disease targets–and Abbott presents some data. Then assume both: optimistically, sales will reach a level of the average of the top five; and conservatively sales will reach the average of all drugs in that area–to give us a feel for the range of sales. For example, cancer and antibiotic markets are highly fragmented, so the average sales of a particular drug is likely small, perhaps less than $100 million. The average sales of the top five drugs may also be less than $500 million, less than half of Abbott's projected sales. Of course, we must still take into account the average probabilities that the drugs not fail in clinical trials and reach the marketplace.

2) In this scheme, we try to estimate sales, and probabilities more from "first principles." Start with Abbott's sales estimates and adjust them downward based on market risk factors. The average probabilities that the drugs ever reach the marketplace must be separately taken into account, and should be adjusted upward or downward based on clinical trials risk factors.

The clinical trials risk factors are:

- uncertainties about the targets key role in the disease (would adjust downward the probability that the drug reaches the marketplace)
- uncertainties about toxicity (would adjust probability downward)

- easily defined or fuzzy clinical trial endpoints (would adjust probability upward or downward). For example, antibiotics have easy endpoints--the patient get better and no evidence of infection; cytostatic drugs have difficult to measure endpoints when in combination with traditional drugs.

We would adjust the development phase probabilities using factors ct_i which range from perhaps zero to above one. We would need to define the appropriate adjustment factors

The market risk factors are:

- number of competitors
- efficacy and side-effects of Abbott's drug vs. competitor's drugs
- cost of Abbott drug vs competitor's drugs
- market need, dire to modest

We would adjust downward Abbott's sales estimates using factors mr_i between zero and one.

Of course determining the ct_i and mr_i factors is somewhat guess work, but at the very least the effort would allow us to better focus on the issues and get some idea of value and risk of the package.

Thoughts on the investment risk spectrum:

- *Example of a zero risk approach:* If Hancock received a guaranteed return on its investment each year increasing yearly regardless of sales, so that the internal rate of return was significant (e.g., 15%), there would be no risk but also no upside reward. One way of receiving the return would be for it to start, for example, in 2003 and ramp up to a maximum in 2015 and decline over the next five years. Under this scenario, Abbott would be paying return from the anticipated drug sales, and Abbott would experience all the up-side and down-side. Hancock would have no risk.

- *Example of an intermediate risk approach*: Receive a guaranteed internal rate of return of for example 5% to 7% as in the above, and receive the rest of the return based on actual sales, so upside potential exists. In this model with a 7% return, one could perhaps even take Abbott's likely inflated sales estimates, since it is all upside above 7%. This removes much of the uncertainly of estimates of eventual sales.

- *Highest risk approach:* Hancock does its best to estimate what it expects for sales on the drug basket, makes the appropriate investment with an appropriate royalty rate, and receives all its return as royalty on actual sales.

An idea for simplifying the financial calculations of appropriate investment amount and royalty rate to give an acceptable internal rate of return (IRR) to Hancock.

Since all the drugs in the basket which are in clinical trials are about the same phase of clinical trials (this excludes all the cytostatic agents except one) begin sales approximately between 2003-2005 and ramp up to maximum sales in approximately 2010-2013, and patents expire about 5 years later, we could use the linear IRR model developed at present only for single drugs by treating the package as a single drug, with total sales and average probability.

This will be a quick and dirty way, and likely as good as a more detailed model, to get in the range of reasonable royalty return.

Confidential Property of John Hancock
(prepared by Lynn C. Klotz, PhD)

Summary Profile of the Basket

Drug	Disease Targets	Mechanism of Action	Stage of Development	Preliminary Assessment Promise/ Market-risk	Projected Maximum Sales
ABT-980	benign prostatic hyperplasia (BPH)	alpha 1a adrenoceptor antagonist	phase II completed, phase III begun?	high/ medium	$700 mil. (worldwide)
ABT-627	cytostatic therapy for hormone resistant metastatic prostate cancer (PCA)	endothelin ET-1 antagonist for Eta receptor	phase II completed, phase III begun?	medium/ medium	$1,000 mil. (worldwide)
ABT-773	bacteria resistant to present antibiotics	new class of antibiotics (ketolides)	phase III?	high/ low	$1,000 mil. (worldwide)
ABT-594	diabetic neuropathic pain	cholinergic channel modulator (chCM)	phase IIa, Phase IIb about to begin	high/ medium	$1,100 mil. (worldwide)
A-254751	cytotoxic therapy for late stage breast, NSCL, ovarian, and pancreatic cancers	binds to the colchicine site on tubulin to inhibit microtubule formation	preclinical or phase I?	high/ high	$680 million (worldwide)
ABT-518	cytostatic therapy for late stage breast, NSCL, ovarian, and pancreatic cancers	matrix metallo proteinase inhibitor (MMPI)	preclinical or phase I	high/ high	$850 mil. (worldwide)
FTI	same as ABT-518	farnesyl-transferase inhibitors which block either farnesylation of RAS or RhoB	early preclinical?	high/ high	$850 mil. (worldwide)
Uro-kinase inhib-itors	same as ABT-518	serine protease inhibitor	early preclinical	high/ high	$850 mil. (worldwide)

Note to table: Market risk, in this preliminary assessment is a qualitiative "feel" based on uncertainties in technical strategy, uncertainties in clinical trials, perceived value of the drug compared to others, number of competitors.

Issues, Questions, Evaluation Tasks

ABT-980 (alpha 1a adrenoceptor antagonist for BPH).

Product is scheduled to begin Phase III clinical trials in second quarter 2000. Has it begun Phase III? What were the results of Phase II?

According to Abbott, uroselective agents such as Tamsulosin (Flomax®) and ABT980 are predicted to be the standard of care replacing existing non-selective agents. We should search the literature for a confirmation of that statement, and understand the medical communities view of selective vs non-selective agents and competitor potential of Flomax.

At time of ABT980 launch, Abbott expects competition from several other alpha 1a blockers. Abbott lists three key competitive drugs in clinical trials, one lead competitor/drug is Yamanuchi/Glaxo's drug Dutasteride which is in Phase III trials. As a "spot check," we should learn what we can about the status and promise of that drug?

ABT 627 (endothelin ET-1 antagonist for Eta receptor for metastatic prostate cancer).

Abbott classifies this drug as a cytostatic agent not a cytotoxic agent, because it only retards progression of PCa and doesn't cure it. Abbott is positioning it as a drug that delays progression and improves quality of life for HRPCa patients. In clinical trials, quality of life is a somewhat fuzzy endpoint, but some measure can be achieved. Since prostate cancer usually progresses slowly, measuring a delay in progression may be difficult in clinical trials? What effect will this have on FDA's assessment?

Has the drug yet entered Phase III trials, if so when? Are preliminary data available? Is it the only Abbott cytostatic agent in advanced clinical trials?

The drug is in Phase I trials for other cancer types. Animal studies (Abbott's or general literature knowledge?) indicate that there is potential for other non-cancer conditions? Would Hancock receive royalties for these too; put another way, is Hancock buying royalty shares for all sales of the compound, or for just prostate cancer?

For advanced PCa, hormone therapy is the main treatment, but treatment becomes ineffective after two to three years with reduced life expectancy of only 12 months, and no chemotherapy has shown promise for these patients. Perhaps we should "spot-check" the accuracy of these statements. (Patients resistant to hormone therapy are called HRPCa.)

Novatrone (Novantrone/Immunex) is the only drug for HRPCa with pain. We should perhaps ascertain its promise as a competitor, as a "spot-check" on Abbott's reasoning.

Confidential Property of John Hancock
(prepared by Lynn C. Klotz, PhD)

Are there enough HRPCa patients to justify Abbott's $1 billion projected sales of the drug, especially since there are at least 10 competitive drugs in advanced clinical trials? How will PSA testing eventually reduce the number of patients with metastatic disease? I believe it has a great success in the US.

ABT-773 (a new class of antibiotics for bacteria resistant to present antibiotics)

We should MedLine and business database search ketolide antibiotics to independently determine their promise. Then an expert like Stuart Levy should be consulted. Andy Onderdonk might also be able to supply the names of experts for us.

Phase II clinical trial results look impressive to me: highly efficacious against four bacteria. Why did they pick those four bacteria? Since the multicenter phase II clinical trials were completed in April 1999 and the data have been analyzed, the drug should be in phase III. Is it? How far along?

Antibiotic clinical trials are relatively straight forward, the infection disappears and the patient gets better in short time.

Adventis' ketolide (telithromycin/Ketek) is ahead with an NDA filed 3/00. Has it been approved?
How does Abbott's ketolide compare?

ABT-594 (cholinergic channel modulator (chCM), initial indication is for diabetic neuropathic pain).

The drug, according to Abbott, is expected to be the first cholinergic channel modulator on the market. How promising is this approach compared to others? We should look at the phase IIa results.

There may be a problem with the therapeutic window. Phase I studies indicated a maximum tolerated dose of 150 ug/day for an oral formulation. Abbott says for capsules results "suggest that higher doses can be tolerated." How much higher? Phase IIa studies suggest "a trend towards analgesic effect at 75 ug bi daily (BID). Thus, the therapeutic window may only be slightly greater than one, and about 10% of patients at 75 ug BID had a number of uncomfortable side effects such as headaches, nausea, etc. There appears to be some risk of not passing phase II clinical trials. We should perhaps get an assessment from a pain clinical-trials expert.

While the initial indication is narrowly defined as diabetic neuropathic pain, the ultimate market is for neuropathic chronic pain in general. This is an underserved market accrding to Abbott.

Pregabalin/Park-Davis is in Phase III (for neuropathic pain?) and is expected to be introduced in 2001. GV 196771 Glaxo is in phase II for neuropathic and chronic pain. These appear to be serious competitors, we should learn what we can about them from the literature, and an expert assessment.

A-254751 (binds to the colchicine site on tubulin to inhibit microtubule formation, for MDR resistant tumors)

The drug "inhibits the *in vitro* polymerization of microtubules." Also inhibits a broad spectrum of tumor-derived human cell lines including those that are pacitaxel and doxorubicin resistant due to MDR and other phenotypes. This meets a important market need.

In animal synergic (definition?)and xenograft models, "A-254751 demonstrated impressive oral anti tumor activity."

In dogs, there have been adverse cardiovascular effects (caused by vasoconstriction?), that have not been observed in patients. Does this mean that Phase I trials are underway, completed?

Abbott states that it will thoroughly quantify the risk from vasoconstriction in humans caused by intermittent and repeated dosing of the drug. The drug may well present too big a risk to humans and not make it out of phase I. What is Abbott's current status and assessment of the drug?

There are seven competitive colchicine site ligands in development by competitors. Three have been abandoned in Phase I (not safe) and one in phase II (why?). Three are still actively being developed. This both highlights the safety risk and the promise. We need a cancer experts assessment of the safety and promise of the approach (either Peter Glazer or someone he recommends).

I am surprised that their maximum sales estimate is less than $1 billion, as drugs that are effective and can defeat MDR should find high usage in a total cytotoxic market of over $7 billion.

ABT-518 (matrix metallo proteinase inhibitor program, cytostatic therapy for late stage breast, NSCL (non-small cell lung cancer), ovarian, and pancreatic cancers)

The MMP enzymes are elevated in cncer and are associated with the ability of cancers to metastasize. Inhibitors of MMP's may suppress tumors by suppessing invasion of the cancer into the blood and they may also suppress angiogenesis. Since they don't attack the tumor cells themselves, they are called cytostatic agents and represent chronic therapy. These may be small

molecule competitors to EntreMed's (Folkman's lab) angiogenesis drugs.

Abbott states that there are more than 200 compounds in development for cytostatic targets.

This is a program targeting gelatinase A and gelatinase B, because Abbott claims these two MMP's are particularly important in tumor progression. We should see what the literature says about the promise of gelatinase targeting as opposed to other enzymes involved in invasion.

Would Hancock's rights extend to all MMP inhibitors developed in the program or be limited to ABT-518?

Therapeutic window of 20 in rats bodes will to the drug.

These agents have the advantage that they can be given in combination with current therapy, so the FDA may allow clinical trials on early-stage cancer patients which would expand potential market too. In addition, in my view, these add-on combination therapies have unusual promise- but are high market risk because they are new.

AB518 has been tested in animals with good pharmacokinetics and toxicology.

Abbott expects sales to begin in 2006 peaking in 2012. This means the whole clinical trial process will take about 6 years which is about right for trials today. Will this drug enter Phase I this year, so that the time schedule can be met?

FTI program (farnesyltransferase inhibitors which either block farnesylation of RAS or RhoB, cytostatic therapy for late stage breast, NSCL, ovarian, and pancreatic cancers)

These agents appear to inhibit angiogenesis, and so are cytostatic agents.

According to Abbott, "farnesyltransferase inhibitors have demonstrated impressive anti tumor activity in preclincal models with activity equivalent to or better than that achieved with conventional cytotoxic chemotherapy given at maximal tolerated dose."

This approach is validated by the fact that there are 12 competitor drugs in development, five in clinical trials. Abbott may be late in a crowded field. Janssen Pharmaceutica/R-11577 is in Phase III and Schering-Plough/Sch66336 is in Phase II. We should learn about the promise of these two drugs, both to assess the real promise of the approach and the potency of the competition.

While Abbott is not yet in clinical trials, has it picked a promising candidate?

Urokinase inhibitor program (serine protease that activates plasminogen to plasmin which breaks down basement membrane and interstitial matrix, cytostatic therapy for late stage breast, NSCL, ovarian, and pancreatic cancers)

Urokinase breaks down basement membrane and interstitial matrix required for tumor growth and metastasis.

Abbott's urokinase program is more advanced than competitors (at least seven competitors in preclinicals) with potency 20 fold more than nearest competitor.

Again, the number of competitors developing urokinase inhibitors validates the approach.

KLOTZ DEPOSITION EXHIBIT 8

D'S EXHIBIT 551

From: Lynn C. Klotz [LynnKlotz@compuserve.com]
Sent: Tuesday, June 27, 2000 8:52 PM
To: Blewitt, Stephen
Subject: Materials for your comments

Steve,

I spent the whole day today literature searching for abstracts in all cancer areas relating to Abbott's drug basket. At this point, I have read and have a good feeling for the state of research and drug development in the cytostatic area in geenral and for the endothelin ET-1 antagonist (ABT-627). I have identified experts for interviews in both areas, and have generated lists of questions for both the experts and Abbott. Attached are several files:

** intro-statement: My draft cover story for expert interviews. Please review.

**abbott-cytostatic: Interview candidates and questions for experts and Abbott. After your edits, you may wish to e-mail Abbott their questions, or alternatively save them for your next encounter with them. Perhaps a conference call among you, me and Abbott would be an efficient way to introduce the questions. Of the many abstracts I read, I have included in this file some that might help you get up to speed on the thinking in cytostatic agents and ET-1 antagonists.

**abbott-bask: This is the same one I sent you last week. I have made a few corrections to the Table, so I am resending it.

The bottom line is that cytostatics is an area of high promise, but there are issues: proof that it will deliver and clinical trial endpoint issues, are the two main ones.

My plan is to start interviews in these two areas, before reading and condensing my research into the other cancer areas. After the cancer drugs, I will tackle the other non cancer drugs.

When, you look at this material, let's talk

- Lynn

EXHIBIT
8
KLOTZ
11-16-06
PENGAD 800-631-6989

CONFIDENTIAL
JH 003058

Introductory Statement to Interviewees

file: intro-statement

I am a consultant for the investment arm of John Hancock Mutual Insurance Company. John Hancock is considering an investment in a major pharmaceutical company. As part of its due diligence, John Hancock must understand something about the pharmaceutical company's drugs both on the market and in development and the competitive situation for both.

I am trying to understand the promise and issues with drugs in development in your area of expertise [***name area****], may I schedule a half-hour of your time to ask you some questions over the telephone? John Hancock is willing to give you an honorarium of $150 for your help.

Cytostatic Agents in General and Particular Abbott Drugs and Targets

file: abbott-cytostatic

Cytostatic agents in general

Potential interviewees for cytostatic therapies:

These interviews will take 45 minutes. I believe the NCI people cannot accept an honorarium. I will offer $150 for ½ hour and $225 for 3/4 hour honorarium to non-NCI interviewees. If serious questions remain after three interviews, I will interview one or two more experts.

Carol Dahl, NCI (She is high up in the NCI, works closely with, and reports to Richard Klausner, the Director of NCI.

Lance Liotta, Laboratory of Pathology, NCI, or one of his colleagues, such as EC Kohn. (Liotta is a highly regarded cancer researcher. See his insightful review article below.)

L. Rosen, University of California Los Angeles School of Medicine, Los Angeles, California 10945, USA. LSROSEN@mednet.ucla.edu. He has written a recent review article (see below) in which "The developmental status of angiogenesis inhibitors in human clinical trials is presented," I will get a copy of his paper too.

Questions for experts in cytostatic therapies

Do you see cytostatic therapies being used only on advanced disease? On all disease? Mainly in combination with traditional cytotoxic therapies? Will cytostatic therapies play a role as adjuncts to surgery and radiation therapy as well?

My understanding is that the overall mortality due to metastatic cancer has not or only minimally been reduced in spite of intensive research, does this represent a big opportunity for cytostatic therapies? How likely is it, in your opinion, that cytostatic therapies will provide big improvements in treatment of metastatic cancers?

One literature review indicated that approximately thirty cytostatic agents for angiogenesis alone are undergoing clinical trials, and another fifty agents preclinical testing. Cytostatic drug development is a crowded field. Which of the large drug companies do you perceive as leaders in this area?

There are many approaches to cytostatic therapy, such as matrix metalloproteinase inhibitors, angiogenesis inhibitors, farnesyltransferase inhibitors, and tyrosine kinase inhibitors, serine protease inhibitors (e.g., urokinase inhibitors), endothelin ET-1 antagonists (bind to ETA receptors). Is there one approach that seems most promising? Least promising? How would you rank them? Is it too early to tell? Which are the most promising candidates?

Matrix metalloproteinase inhibitors seems to be an especially competitive area and have been under development for a long time. Could a highly successful matrix metalloproteinase inhibitor kill the opportunities for cytostatic drugs aimed at the other targets?

What is known about cost-effectiveness of cytostatic agents? I ask this because one literature pharmacoeconomic study indicated that cytostatic treatment with Interferon-alpha for multiple myeloma was not cost effective when quality-life-years was used as a measure, because of the drugs toxicity.

Since cytostatic therapies don't kill tumor cells, the use of time to progression (TTP) of disease seems to be the necessary clinical trials measure? What are the problems with this measure? Do you think the diofficulty of measuring TTP will prolong clinical trails and even cause some drugs to fail to get approval? How serious an issue is this?

<u>Questions for Abbott about cytostatic therapies in general</u>

One literature review indicated that approximately thirty angiostatic agents are undergoing clinical trials, with another fifty agents in preclinical testing. This is a crowded field. While Abbott's approaches are clearly cutting-edge, how can Abbott achieve a large market share given the large number of competitors in this area?

Sugen mentions one of their small-molecule compounds, the angiogenesis inhibitor SU5416, that is about to enter Phase III trials for non-small-cell lung cancer. This seems to be well advanced in development. What is the status of this drug? Do you see it as a serious competitor? Are there other drugs for your disease indications that are well-advanced in clinical trials? How are the abbott early development candidates superior?

Have you considered pharmacoeconomics of your cytostatic approaches yet, e.g,
cost utility = (long-term-cost)/(quality-life-years-saved)? In particular, if there are side-effects, quality life years saved may be much less than simply life years saved.

One literature review indicated that approximately thirty angiostatic agents are undergoing clinical trials, with another fifty agents in preclinical testing. This is a crowded field. While Abbott's approaches are clearly cutting-edge, how can Abbott achieve a large market share given the large number of competitors in this area?

Questions for Abbott and Interviewees on ABT-627

<u>Potential interviewees:</u>

I plan two one-half hour interviews.

Nelson JB or Carducci MA, The James Buchanan Brady Urological Institute, The Johns Hopkins

Oncology Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA. nelsonjb@msx.upmc.edu. This e-mail address is for the University of Pittsburgh. Is he there or at Johns Hopkins, since he seems to publish in both places?

Ripple GH, Wilding G (wrote a recent review: Drug development in prostate cancer.)

Alternates:
Hsu JY, Pfahl M, Sidney Kimmel Cancer Center, San Diego, California 92121, USA.

Kroodsma JM, Rabelink AJ, Academisch Ziekenhuis, afd. Nefrologie, Utrecht.

Questions for ABT-627 interviewees

What is the evidence that blocking endothelin receptors will have clinical value in the treatment of metastasized prostate cancer?

Is blocking the ETa receptor with an endothelin-1 (ET-1) antagonist the best strategy?

The literature mentions several drugs mostly by alpha-numeric name: BQ-123, A127722, ABT-627, Novantrone (already on market), and retinoids (which reduces ET-1 transcription). Do you have an opinion on the promise and issues with these drugs? Which companies are developing these drugs?

The Japanese company Yamanouchi supposedly has a drug in clinical trials? Name? Targets? Promise? Clinical trial status?

What other targets for slowing metastasis of prostate cancer are promising? For example, would an inhibitor targeting the ET-1 converting enzyme phosphoramidon be a good target? Other targets in the pathway to metastasis?

One literature study indicated that a number of factors: 1beta (IL-1beta), tumour necrosis factor alpha (TNF-alpha) and transforming growth factor beta (TGF-beta) stimulated ET-1 and big ET-1 secretion, is there merit to targeting any of these to slow metastasis?

Do you think a drug that successfully slows metastasis of prostate cancer would be widely used? For which patients would such a drug be prescribed? What percentage of prostate cancer patients fall into that category? What number of quality-life-years might such a drug provide?

Drugs that slow metastasis, angiogenesis, etc. that don't usually kill the cancer cells have been dubbed cytostatic therapy? In general, how promising is cytostatic therapy? Has its value been proven anywhere?

Questions for Abbott

The literature mentions Is A127722 an Abbott compound? Is it in the development pipeline? What are its prospects compared to ABT627?

The literature mentions other ET-1 related drugs, for example BQ-123 and retinoids (which reduces ET-1 transcription), do you have an opinion on the promise and issues with these drugs? Which companies are developing these drugs?

You predict a billion dollar market of A-627, yet its on-the-market competitor Novantrone has only a relatively stagnant market of only $35 million. Is this because you liken ABT-627 to hormone therapies? Could you break down the potential market for A-627 for us? For which patients would it be prescribed? What percentage and yearly number of prostate cancer patients fall into that category?

Have you carried out any pharmacoeconomics analysis? What additional quality-life-years might such a drug provide? Will the cost be low enough to be cost effective?

Selected Literature Abstracts

<u>Especially informative articles about cytostatic therapies in general</u>

My comments are in *italics*.

18: Cancer Res 1995 May 1;55(9):1856-62
Molecular insights into cancer invasion: strategies for prevention and intervention.
Kohn EC, Liotta LA, Laboratory of Pathology, National Cancer Institute, NIH, Bethesda, Maryland 28092, USA.
(*Liotta is a highly regarded cancer researcher. We should interview him or someone from his lab. Get suggestions on whom to interview from Carol Dahl. This particular article, however, is old.*)
The diagnosis and treatment of solid tumors usually begins at a late stage when most patients already have occult or overt metastasis. Many years of cancer progression precede diagnosis of most solid tumors. Novel noncytotoxic therapeutics may be specially suited for administration during this interval. An important window of intervention can be defined as the period during which transition from a hyperproliferative state to acquisition of the capacity for invasion and metastasis occurs. Investigation of the molecular basis of invasion is uncovering strategies for delaying progression of preinvasive carcinoma and treatment of primary tumors and established metastasis. Although tumor cell invasion might not be rate limiting for the growth of metastasis, anti-invasive agents can block tumor angiogenesis and thereby indirectly block metastasis growth. Two classes of molecular anti-invasion targets exist: (a) cell surface and extracellular proteins, which mediate sensing, adhesion, and proteolysis; and (b) signal transduction pathways, which regulate invasion, angiogenesis, and proliferation. Both categories of targets yield treatment approaches that are now being tested in the clinic. Metalloproteinase inhibitors, such as BB94, are based on the recognition that metalloproteinases play a necessary role in invasion and angiogenesis. (*Today–five years later–what is the status of BB94?*) The orally active signal transduction inhibitor carboxyamidotriazole modulates non-voltage-gated calcium influx-regulated signal pathways and reversibly inhibits tumor invasion, growth, and angiogenesis. Blockade of invasion, angiogenesis, or cellular signal pathways is likely to generate a cytostatic, rather than a cytotoxic effect. Cytostatic therapy constitutes an alternative paradigm for clinical translation that may complement conventional cytotoxic therapy. For patients with newly diagnosed solid tumors, long-term cytostatic therapy could potentially create a state of metastasis dormancy or delay the time to overt relapse following cytotoxic agent-induced remission. Clinical toxicity and pharmacology using oral cytostatic agents in phase I trials and in adjuvant settings will provide an important foundation for the translation of this approach to the preinvasive carcinoma period.
Publication Types:
Review
Review, tutorial
PMID: 7728753, UI: 95246023

1: Oncologist 2000;5 Suppl 1:51-4
Clinical strategy for the development of angiogenesis inhibitors.
Carter SK

SUGEN, Inc., South San Francisco, California, USA. star-wescott@sugen.com
Angiogenesis inhibitors differ from conventional cytotoxic chemotherapy agents by targeting normal cells rather than tumor cells, which may contain multiple mutations. Because of this, the traditional strategy used in clinical development of cytotoxic agents may not be appropriate for these novel agents. Many clinical studies are now evaluating these agents with a new approach, referred to as the cytostatic paradigm. The cornerstone of the cytostatic paradigm is the use of time to progression (TTP) of disease as the decision-making criterion for "go/no go" in the early phases of clinical development. However, the use of TTP as the main criterion for clinical trials is complicated for a variety of reasons, including: A) the lack of standardized criteria accepted by regulatory authorities; B) the heterogeneity of the historical database, and C) the larger number of patients needed for the "go/no go" decision-making process. In addition, clinical trials of cytotoxic agents have traditionally used objective response (despite the controversy regarding objective response as a surrogate for clinical activity) as the main criterion for determining whether the results of phase II studies justify the pivotal phase III studies. Another aspect of the clinical development strategy is combining angiogenesis inhibitors with cytotoxic chemotherapy. The rationale for combination of angiogenesis inhibitors with cytotoxic agents is based on: A) different targets for these agents; B) lack of cross-resistance patterns; C) lack of myelosuppression with angiogenesis inhibitors allows administration of full doses of all agents, and D) the assumption that combining these agents will result in additive antitumor activity. Combination therapy with angiogenesis inhibitors may be attractive to both clinicians and their patients because it allows cytostatic agents to be used upfront in treatment while contributing to drug registration strategy (cytostatic/cytotoxic combination therapy versus cytotoxic therapy). The clinical development of the angiogenesis inhibitor SU5416, a small molecule inhibitor of vascular endothelial growth factor, is currently ongoing. In phase I trials, SU5416 demonstrated activity in both colorectal and non-small-cell lung cancer patients. Based on these encouraging results, phase III studies to evaluate combination of SU5416 with established cytotoxic therapy are planned. (*This competitive drug seems to be ahead of Abbott's candidates for NSCL*). These studies will include an interim analysis, the equivalent of a phase II evaluation of clinical activity. If successful, this strategic approach will save significant time in the clinical development process.
PMID: 10804092, UI: 20264300

2: Oncologist 2000;5 Suppl 1:20-7
Antiangiogenic strategies and agents in clinical trials.
Rosen L
University of California Los Angeles School of Medicine, Los Angeles, California 10945, USA. LSROSEN@mednet.ucla.edu
The understanding that the growth of tumors depends on the acquisition of a blood supply has led to the development of new therapies for cancer and other angiogenic diseases based on inhibition of neovascularization. This review examines the role of angiogenesis in cancer progression and describes various strategies for interfering with this process. The developmental status of angiogenesis inhibitors in human clinical trials is presented, including their proposed mechanisms of action. (*This statement indicates this person should be interviewed, especially since this is a brand-new paper, but e-mail him to try to get a copy of the paper first.*) Standard chemotherapeutic agents and angiogenesis inhibitors are compared, noting that different end points might need to be considered in clinical trials and that drug resistance may be less of a problem with antiangiogenic

therapy than with conventional chemotherapy regimens. The suggestion is made that cytotoxic chemotherapy and angiogenesis inhibitors used in combination may produce complementary therapeutic benefits in the treatment of cancer.
Publication Types:
Review
Review, tutorial
PMID: 10804087, UI: 20264295

13: Curr Pharm Des 2000 Mar;6(4):417-39
Angiogenesis: new targets for the development of anticancer chemotherapies.
Gourley M, Williamson JS
Department of Medicinal Chemistry, University of Mississippi, Mississippi, MS 38677, USA.
(Perhaps the medicinal chemisitry perspective would be useful to us.)
Angiogenesis is the process by which new blood vessels are formed from preexisting microvasculature. To ensure an adequate blood supply, tumor cells release angiogenic factors that are capable of promoting nearby blood vessels to extend vascular branches to the tumor. In addition, larger tumors have been shown to release angiogeneic inhibitory factors that prevent blood vessels from sending branches to smaller, more distant tumors that compete for oxygen and nutrients. Angiogenesis is a complex multistep biochemical process, and offers several potential molecular targets for non-cytotoxic anticancer therapies. Strategies for exploiting tumor angiogenesis for novel cancer drug discovery include: (i) inhibition of proteolytic enzymes that breakdown the extracellular matrix surrounding existing capillaries; (ii) inhibition of endothelial cell migration; (iii) inhibition of endothelial cell proliferation; (iv) enhancement of tumor endothelial cell apoptosis. There is also a host of miscellaneous agents that inhibit angiogenesis for which the specific mechanisms are not clear. Several methods have been developed for measuring antiangiogenic activity both in vitro and in vivo. Although there has been intensive research efforts focused at the phenomena of angiogenesis, as well as the search for antiangiogenic agents for more than two decades, many questions remain unanswered with regard to the overall biochemical mechanisms of the angiogenesis process and the potential therapeutic utility of angiogenic inhibitors. Nevertheless potent angiogenic inhibitors capable of blocking tumor growth have been discovered, and appear to have potential for development into novel anticancer therapeutics. However there are still hurdles to be overcome before these inhibitors become mainstream therapies.
Publication Types:
Review
Review, academic
PMID: 10788590, UI: 20251313

Especially informative articles about endothelin receptor antagonist field and advanced prostate cancer

My comments in *italics*.

6: Semin Oncol 1999 Apr;26(2):217-26
Drug development in prostate cancer.
Ripple GH, Wilding G
Department of Medicine, University of Wisconsin Comprehensive Cancer Center, Madison, USA.
Despite strategies aimed at early detection and treatment, prostate cancer remains a leading cause of morbidity and mortality among males. Current therapies have limited impact on the natural history of metastatic hormone-refractory prostate cancer (HRPC). With an improved understanding of tumor biology, including apoptosis, differentiation, cell cycling and signaling, and angiogenesis, many potential new targets for therapy have been unveiled. Modulation of these processes may result in cytotoxic or cytostatic effects. The evaluation of therapies based on manipulation of these targets may not be adequately addressed by current study designs and traditional parameters of efficacy. Examples of agents currently in clinical trials that illustrate some of the challenges presented to clinical investigators include monoterpenes such as perillyl alcohol (POH), vitamin D analogs, flavones such as flavopiridol, and angiogenesis inhibitors. Agents such as these are aimed at unique cellular targets and will require novel approaches to determine their clinical utility. Unfortunately, in the United States, only a small proportion of cancer patients, including prostate cancer patients, are enrolled in clinical trials. We must do better to efficiently assess promising new treatment approaches and improve outcome for our patients.
Publication Types:
Review
Review, tutorial
PMID: 10597732, UI: 20064602

11:Cancer Res 1996 Feb 15;56(4):663-8
Endothelin-1 production and decreased endothelin B receptor expression in advanced prostate cancer.
Nelson JB, Chan-Tack K, Hedican SP, Magnuson SR, Opgenorth TJ, Bova GS, Simons JW
James Buchanan Brady Urological Institute Research Laboratories, Johns Hopkins Hospital, Baltimore, Maryland 21287-2411, USA.
The potent vasoconstrictor endothelin-1 (ET-1) is at its highest concentration in the normal human ejaculate and is associated with the progression of metastatic prostate cancer. ET-1 protein expression is detected in situ in 14 of 14 primary cancers and 14 of 16 metastatic sites of human prostatic carcinoma. Exogenous ET-1 induces prostate cancer proliferation directly and enhances the mitogenic effects of insulin-like growth factor I, insulin-like growth factor II, platelet-derived growth factor, basic fibroblast growth factor, and epidermal growth factor in serum-free conditions in vitro. The ETA-selective receptor antagonist A-127722 (*an Abbott compound?*) inhibits ET-1-stimulated growth, but the ETB-selective receptor antagonist BQ-788 does not. ET-3, an ETB-selective agonist, also had no effect on prostate cancer growth. No specific ETB-binding sites could be demonstrated in any established human prostate cancer cell line tested, and ETB mRNA, detected by reverse transcription PCR, was reduced. The predominance of ETB binding on human

benign prostatic epithelial tissue is not present in metastatic prostate cancer by autoradiography. In human prostate cancer progression to metastases, ET-1 and ETA expression are retained, whereas ETB receptor expression is reduced.
PMID: 8630991, UI: 96223664

6:Cancer Res 1998 Nov 1;58(21):4817-22
ET-1 expression and growth inhibition of prostate cancer cells: a retinoid target with novel specificity.
Hsu JY, Pfahl M
Sidney Kimmel Cancer Center, San Diego, California 92121, USA.
Endothelin-1 (ET-1) is not only a potent vasoconstrictor but also serves as an important growth stimulator in various cancers, including breast, cervical, pancreatic, and prostate cancer. This suggests that blockage of ET-1 production may suppress tumor growth and possibly metastasis. We observed that certain synthetic retinoids, and all-trans-retinoic acid can repress LNCaP prostate cancer cell growth in vitro. In addition, these retinoid compounds counteracted exogenous ET-1-induced growth stimulation. Retinoid-dependent growth retardation of LNCaP cells coincided with suppression of ET-1 gene expression to a level undetectable by reverse transcription-PCR. (*How do the small-molecule retenoid drugs suppress ET-1 gene expression (affect promotor activity, see below)? Is ABT-627 a retenoid compound which works at the level of transscrition, or is a traditional antagonist binding directly to the Eta receptor? Do retenoids represent serius competition to ABT-627? Are they in development and by whom?*) Contrarily, the androgen-insensitive DU145 cells were refractory to retinoid treatment. To investigate the underlying mechanisms of the cell-specific response to retinoids, we transfected ET-1 promoter constructs containing wild-type or mutated AP-1 or GATA-2 site into prostate cancer cells. Distinct regulations of ET-1 promoter activity were found; in LNCaP cells, both binding sites are essential for optimal promoter activation, whereas in DU145 cells, additional promoter sequences and/or transcriptional factors seem to be involved. Furthermore, several anti-AP-1 selective retinoids failed to repress ET-1 promoter activity and to exhibit a cell growth-inhibitory effect on LNCaP cells, suggesting that different retinoid structural configurations are required for the inhibition of an AP-1 complex versus an AP-1/GATA-2 complex.
PMID: 9809984, UI: 99025856

7:Ned Tijdschr Geneeskd 1997 Sep 20;141(38):1806-10
[Endothelins: possibly a new pharmacological approach in cardiovascular diseases, kidney diseases and oncological disorders].
[Article in Dutch]
Kroodsma JM, Rabelink AJ
Academisch Ziekenhuis, afd. Nefrologie, Utrecht.
Only 10 years ago, the vasoconstricting peptide endothelin was discovered; it is produced by endothelial cells. Different isoforms and receptors of endothelin have been identified. The effects of endothelin-I, the most important isoform, are mainly vasoconstriction and proliferation of cells. (*ET-1 is the most important ET isoform*) In the last few years endothelin receptor antagonists have become available, which can delineate the clinical importance of the endothelin system. Possible indications for endothelin receptor blockers are renal disease (acute and chronic renal failure) and cardiovascular disease (heart failure; restenosis after percutaneous transluminal coronary

CONFIDENTIAL
JH 003068

angioplasty (PTCA); pulmonary hypertension; systemic hypertension). There is also a possible role for endothelin receptor blockers in oncology (prostatic carcinoma). (*This 1997 paper talks about possible roles of Eta blockers in prostate cancer.*) Currently clinical trials are being carried out to determine the efficacy of these compounds for the above-mentioned indications. (*Do these authors know of other clinical trials in progress?*)

Publication Types:
Review
Review, tutorial
PMID: 9545734, UI: 98207344

KLOTZ DEPOSITION EXHIBIT 9

D'S EXHIBIT 803

From: Lynn C. Klotz [LynnKlotz@compuserve.com]
Sent: Monday, July 03, 2000 5:01 PM
To: Blewitt, Stephen
Subject: Update on cytostatic area

Steve:

Here are the questions, etc from my research of the cytostatic field (see attachment). The questions for those to be interviewed about general cytostatic agents are in pretty good shape. Please read them and add additional questions if you wish.

This research is time consuming. I have put in about 38 hours so far, but I think worth it, since it provides the background and information for the key issues and questions to be asked. If you want to short cut anything, advise me.

The questions to Abbott definitely need editing, and I don't think we should ask them many of these questions until I have completed the interviews. The answers may become obvious. And a few of the Abbott questions are trivial in the sense that they would satisfy my curiosity on a few points, but no answer would change our view on the investment. I suspect I will eliminate these, since we will have more meaningful questions.

The bottom line is that cytostatic therapies is a hot development area, but there are a number of general issues (e.g., clinical trial endpoints, effectiveness, cost effectiveness, competition, etc.) Most are not yet in clinical trials, so the probability of a particular compound reaching the marketplace is low; therefore, cytostatic therapies are more an up-side on the investment in the rest of the basket.

I will collect contact information and set up interviews from July 5 to July 10 when I am travelling and can find access the internet or make phone calls. I plan to conduct the interviews when I return. We may have 40 potential interviews, which is too many, so we together will need to make some decisions as to what to cut short.

Over the next few days, since I expect most people are away for the holiday, I will continue my literature search into the other basket drugs.

-Lynn

EXHIBIT
9
KLOTZ
11-17-06
PENGAD 800-631-6989

CONFIDENTIAL
JH 003032

CONFIDENTIAL
property of John Hancock

Cytostatic Agents in General and Particular Abbott Drugs and Targets

file: abbott-cytostatic

Cytostatic agents in general

Potential interviewees for cytostatic therapies:

These interviews will take 45 minutes. I believe the NCI people cannot accept an honorarium. I will offer $150 for ½ hour and $225 for 3/4 hour honorarium to non-NCI interviewees. If serious questions remain after three interviews, I will interview one or two more experts.

Carol Dahl, NCI (She is high up in the NCI, works closely with and reports to Richard Klausner, the Director of NCI.

Lance Liotta, Laboratory of Pathology, NCI, or one of his colleagues, such as EC Kohn. (Liotta is a highly regarded cancer researcher. See his insightful review article below.)

L. Rosen, University of California Los Angeles School of Medicine, Los Angeles, California 10945, USA. LSROSEN@mednet.ucla.edu. He has written a recent review article (see below) in which "The developmental status of angiogenesis inhibitors in human clinical trials is presented,"

Questions for experts in cytostatic therapies

Do you see cytostatic therapies being used only on advanced disease? On all disease? Mainly in combination with traditional cytotoxic therapies or as monotherapies? Will cytostatic therapies play a role as adjuncts to surgery and radiation therapy as well?

My understanding is that the overall mortality due to metastatic cancer has not been reduced meaningfully in spite of intensive research, does this represent a big opportunity for cytostatic therapies? How likely is it, in your opinion, that cytostatic therapies will provide big improvements in treatment of metastatic cancers?

There are many approaches to cytostatic therapy, such as matrix metalloproteinase inhibitors, farnesyltransferase inhibitors, and tyrosine kinase inhibitors, serine protease inhibitors (e.g., urokinase inhibitors), endothelin ET-1 antagonists (bind to ETA receptors). Did I miss anything in this list(e.g., other approaches to angiogenesis inhibition)? Is there one approach that seems most promising? Least promising? How would you rank them? Is it too early to tell? Which are the most promising candidates within each approach?

CONFIDENTIAL
property of John Hancock

One literature review indicated that approximately thirty cytostatic agents are in clinical trials to inhibit angiogenesis alone, and another fifty agents are in preclinical testing. Cytostatic drug development is a crowded field. Which of the large drug companies do you perceive as leaders in this area?

Matrix metalloproteinase inhibitors seems to be an especially competitive area and have been under development for a long time. Could a first-on-the-market effective matrix metalloproteinase inhibitor (or any cytostatic agent for that matter) kill the opportunities for cytostatic drugs aimed at the other targets?

What is known about cost-effectiveness of cytostatic agents? My concern stems from three observations:

- They will be administered chronically (daily), which could be expensive;
- in one instance (Marimastat), the drug slowed progression but did not prolong life and has painful joint side-effects, so there are no life-years-save and perhaps no quality-life-years-savedd
- one literature pharmacoeconomic study indicated that cytostatic treatment with interferon-alpha for multiple myeloma was not cost effective when quality-life-years was used as a measure, because of the drugs toxicity.

Since cytostatic therapies don't target killing of tumor cells, the use of time to progression (TTP) of disease seems to be the necessary clinical trials measure? What are the problems with this measure? Do you think the difficulty of measuring TTP will prolong clinical trails or cause some drugs to fail to get approval? How serious an issue is this?

The cancer drug field is traditionally highly fragmented. There are many drugs, so the use of any particular drug is limited. In business terms, this means that sales for an average drug is small, less than $100-$200 million. Yet there are some drugs that do sell over $500 million. Do you have any feel whether there will be cytostatic drugs that will sell above $500 million, or do you expect their use and therefore sales to be limited?

<u>Questions for Abbott about cytostatic therapies in general</u>

One literature review indicated that approximately thirty angiostatic agents are undergoing clinical trials, with another fifty agents in preclinical testing. This is a crowded field. While Abbott's approaches are clearly cutting-edge, how can Abbott achieve a large market share given the large number of competitors in this area?

Sugen mentions one of their small-molecule compounds, the angiogenesis inhibitor SU5416,

CONFIDENTIAL
property of John Hancock

that is about to enter Phase III trials for non-small-cell lung cancer. This seems to be well advanced in development. What is the status of this drug? Do you see it as a serious competitor? Are there other drugs for your disease indications that are well-advanced in clinical trials? How are the abbott early development candidates superior?

Have you considered pharmacoeconomics of your cytostatic approaches yet, e.g, cost utility = (long-term-cost)/(quality-life-years-saved)? In particular, if there are side-effects, quality life years saved may be much less than simply life years saved.

One literature review indicated that approximately thirty angiostatic agents are undergoing clinical trials, with another fifty agents in preclinical testing. This is a crowded field. While Abbott's approaches are clearly cutting-edge, how can Abbott achieve a large market share given the large number of competitors in this area?

CONFIDENTIAL
property of John Hancock

The endothelin ET-1 inhibitor ABT-627

Potential interviewees for ET-1 inhibitors :

I plan two one-half hour interviews.

Nelson JB or Carducci MA, The James Buchanan Brady Urological Institute, The Johns Hopkins Oncology Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA. nelsonjb@msx.upmc.edu. This e-mail address is for the University of Pittsburgh. Is he there or at Johns Hopkins, since he seems to publish in both places?

Ripple GH, Wilding G (wrote a recent review: Drug development in prostate cancer.)

Alternates:
Hsu JY, Pfahl M, Sidney Kimmel Cancer Center, San Diego, California 92121, USA.

Kroodsma JM, Rabelink AJ, Academisch Ziekenhuis, afd. Nefrologie, Utrecht.

Questions for ABT-627 interviewees

What is the evidence that blocking endothelin receptors will have clinical value in the treatment of metastasized prostate cancer?

Is blocking the ETa receptor with an endothelin-1 (ET-1) antagonist the best strategy?

The literature mentions several drugs mostly by alpha-numeric name: BQ-123, A127722, ABT-627, Novantrone (already on market), and retinoids (which reduces ET-1 transcription). Do you have an opinion on the promise and issues with these drugs? Which companies are developing these drugs?

The Japanese company Yamanouchi supposedly has a drug in clinical trials? Name? Targets? Promise? Clinical trial status?

What other targets for slowing metastasis of prostate cancer are promising? For example, would an inhibitor targeting the ET-1 converting enzyme phosphoramidon be a good target? Other targets in the pathway to metastasis?

One literature study indicated that a number of factors: 1beta (IL-1beta), tumour necrosis factor alpha (TNF-alpha) and transforming growth factor beta (TGF-beta) stimulated ET-1 and big ET-1 secretion, is there merit to targeting any of these to slow metastasis?

CONFIDENTIAL
property of John Hancock

Do you think a drug that successfully slows metastasis of prostate cancer would be widely used? For which patients would such a drug be prescribed? What percentage of prostate cancer patients fall into that category? What number of quality-life-years might such a drug provide?

Drugs that slow metastasis, angiogenesis, etc. that don't usually kill the cancer cells have been dubbed cytostatic therapy? In general, how promising is cytostatic therapy? Has its value been proven anywhere?

There are many approaches to cytostatic therapy, such as matrix metalloproteinase inhibitors, farnesyltransferase inhibitors, and tyrosine kinase inhibitors, serine protease inhibitors (e.g., urokinase inhibitors), endothelin ET-1 antagonists (bind to ETA receptors). Did I miss anything in this list(e.g., other approaches to angiogenesis inhibition)? Is there one approach that seems most promising? Least promising? How would you rank them? Is it too early to tell? Which are the most promising candidates within each approach?

One literature review indicated that approximately thirty cytostatic agents are in clinical trials to inhibit angiogenesis alone, and another fifty agents are in preclinical testing. Cytostatic drug development is a crowded field. Which of the large drug companies do you perceive as leaders in this area?

<u>Questions for Abbott on ABT-627</u>

The literature mentions Is A127722 an Abbott compound? Is it in the development pipeline? What are its prospects compared to ABT627?

The literature mentions other ET-1 related drugs, for example BQ-123 and retinoids (which reduces ET-1 transcription), do you have an opinion on the promise and issues with these drugs? Which companies are developing these drugs?

You predict a billion dollar market of A-627, yet its on-the-market competitor Novantrone has only a relatively stagnant market of only $35 million. Is this because you liken ABT-627 to hormone therapies? Could you break down the potential market for A-627 for us? For which patients would it be prescribed? What percentage and yearly number of prostate cancer patients fall into that category?

Have you carried out any pharmacoeconomics analysis? What additional quality-life-years might such a drug provide? Will the cost be low enough to be cost effective?

CONFIDENTIAL
property of John Hancock

The matrix metalloprotease inhibitor (ABT-518)

Potential interviewees for ABT-518

Heath EI, Grochow LB, Division of Medical Oncology, Johns Hopkins Oncology Center, Baltimore, Maryland 21231, USA. heathel@jhmi.edu

Yip D, Ahmad A, Karapetis CS, Hawkins CA, Harper PG
Department of Medical Oncology, Guy's Hospital, London, United Kingdom.

Alternates:

Wojtowicz-Praga S, Theradex, Princeton Junction, New Jersey, USA.
(*If this company is not a drug company, these authors may be good interview candidates? I should internet search this company.*)

Rosemurgy A, Harris J, Langleben A, Casper E, Goode S, Rasmussen H
University of South Florida, Department of Surgery, Tampa, USA.

Questions for ABT-518 interviewees

It has been reported that Marimastat had no survival advantage when compared to chemotherapy with gemcitabine in advanced pancreaic cancer. With no survival advantage, would the FDA be skeptical about the value of slower progression of the disease, especially since there are serious joint-pain side effects (reduction in quality of life). To play devil's advocate, you could argue that not prolonging the patient's life and at the same time inflicting pain why should the FDA approve this drug? Could failure for approval of Marimastat make the approval barriers higher for follow on drugs?

Are there any particular MMP targets where joint pain might be less an issue (e.g, collagen, gelatinases, stromelysin)? What does Marimistat target?

How many different targets have been identified for MMPI inhibitors? Some I know of are collagenases, gelatinases, stromelysin. What are the most interesting targets? Do any appear to be superior, inferior?

Several compounds have entered phase III combination therapy trials and others are in trail alone. What is the latest data? Especially promising compounds or results? Any new issues?

I assume that most MMPI's must be given chronically (daily?), and therefore oral administration is greatly preferred, have any of the MMPI's you are aware of have any pharmacokinetic issues

CONFIDENTIAL
property of John Hancock

(e.g. reduced bioavailability from adsorption to food)?

Do you think a drug that successfully slows metastasis would be widely used? For which patients would such a drug be prescribed? What percentage cancer patients fall into that category? What number of quality-life-years might such a drug provide? What kinds of sales would you expect for a successful MMPI in cancer?

Drugs that slow metastasis, angiogenesis, etc. that don't usually kill the cancer cells have been dubbed cytostatic therapy? In general, how promising is cytostatic therapy? Has its value been proven anywhere?

I have read that vertebrate collagenase was discovered in 1962; and within a few short years, several inhibitors had been identified. Every major drug company has had an MMP inhibitor program in the past, but in 1999, there is only one such product on the market. Why has the market not materialized? Why the renewed interest? What is the product on the market? For what indication?)

There are many approaches to cytostatic therapy, such as matrix metalloproteinase inhibitors, farnesyltransferase inhibitors, and tyrosine kinase inhibitors, serine protease inhibitors (e.g., urokinase inhibitors), endothelin ET-1 antagonists (bind to ETA receptors). Did I miss anything in this list(e.g., other approaches to angiogenesis inhibition)? Is there one approach that seems most promising? Least promising? How would you rank them? Is it too early to tell? Which are the most promising candidates within each approach?

One literature review indicated that approximately thirty cytostatic agents are in clinical trials to inhibit angiogenesis alone, and another fifty agents are in preclinical testing. Cytostatic drug development is a crowded field. Which of the large drug companies do you perceive as leaders in this area?

<u>Questions for Abbott on ABT-518</u>

It has been reported that Marimastat had no survival advantage when compared to chemotherapy with gemcitabine in advanced pancreaic cancer. With no survival advantage, would the FDA be skeptical about the value of slower progression of the disease, especially since there are serious joint-pain side effects (reduction in quality of life). To play devil's advocate, you could argue that not prolonging the patient's life and at the same time inflicting pain why should the FDA approve this drug? Could failure for approval of Marimastat make the approval barriers higher for follow on drugs?

What evidence do you have that the gelatinase inhibitors might not have the joint-pain dose-limiting issues?

CONFIDENTIAL
property of John Hancock

What is the current clinical trial status of competitor's drugs? Marimistat? Prinomastat? BMS275291? Others? Especially promising compounds or results? Any new issues?

In one of their publications British Biotech (the developer of Marimistat) makes special mention of gelatinase. Does that mean that British Biotech is also working on gelatinase inhibitors?

With a potential market for lifelong therapy in rheumatoid arthritis, osteoarthritis, periodontal disease, osteoporosis would Hancock have rights to these additional markets for ABT-518? Or are uses for the gelatinase ABT-518 limited?

Abbott argues since its MMP inhibitors target gelatinase a and b, they may not cause the joint side effects. What data do you have to confirm this?

Some compounds mentioned in one review article are batismastat, marimastat, BAY12-9566, AG-3340, OPB-3206, KBR-7785, KBR-8301, CDP-845(CT-1746), metastat and AE-941 (Neovastat). It was mentioned that many of these are in clinical trials. How many are in trials for cancer?

CONFIDENTIAL
property of John Hancock

Farnesyltransferase inhibitors (FTI)

Potential interviewees for FT inhibitors

Sun J, Blaskovich MA, Knowles D, Qian Y, Ohkanda J, Bailey RD, Hamilton AD, Sebti SM (*possible interview candidates*)
H. Lee Moffitt Cancer Center and Research Institute, Department of Biochemistry and Molecular Biology, University of South Florida, Tampa 33612, USA.

Lebowitz PF, Prendergast GC
(*a good interview candidate, but Prendergast is with DuPont.* Maybe interview Lebowitz.)
The Wistar Institute, Philadelphia, Pennsylvania 19104, USA.

Rowinsky EK, Windle JJ, Von Hoff DD
(*good interview candidate*)
Institute for Drug Development, Cancer Therapy and Research Center, San Antonio, TX 78229-3272, USA. erowinski@saci.org

Questions for interviewees on FTI's

Do FTI's generally work better in combination therapy of monotherapy?

Several compounds have entered clinical trials? Are they combination therapy trials, or monotherapy? What is the latest data? Especially promising compounds or results? Any new issues?

What kinds of sales would you expect for a successful FTI inhibiitor, given that the cancer drug market is traditionally highly fragmented and the competition for FTI is considerable?

Besides farnesyltransferase, geranylgeranyltransferase seems to be a similar target for FTI-like inhibitors. What are the advantages of each target?

There are many approaches to cytostatic therapy, such as matrix metalloproteinase inhibitors, farnesyltransferase inhibitors, and tyrosine kinase inhibitors, serine protease inhibitors (e.g., urokinase inhibitors), endothelin ET-1 antagonists (bind to ETA receptors). Did I miss anything in this list(e.g., other approaches to angiogenesis inhibition)? Is there one approach that seems most promising? Least promising? How would you rank them? Is it too early to tell? Which are the most promising candidates within each approach?

One literature review indicated that approximately thirty cytostatic agents are in clinical trials to inhibit angiogenesis alone, and another fifty agents are in preclinical testing. Cytostatic drug

CONFIDENTIAL
property of John Hancock

development is a crowded field. Which of the large drug companies do you perceive as leaders in this area?

Questions for Abbott on FTI's

In one literature study reported by Abbott, the FTI, A-170634, was studied and favorable results in nude mice were obtained. This is not the one that Abbott abandoned which was ABT 839. What is the status of A-170834?

To which inhibitors will Hancock have royalty rights?

The literature mentions several peptidomimetic inhibitors. Are Abbott's inhibitors peptidomimetics? If so, what is the molecular weight range and production cost?

Several FTI's are mentioned in the literature (A-170634, FTI (SCH 56582--a Schering Plough designation but not the one which is in Phase II clinical trials), L-744,832 FTI-2148, FTI-2153), are these expected to enter trials?

Do FTI's generally work better in combination therapy of monotherapy? Will Abbott's enter trials in combination with a traditional cytotoxic drug?

What kinds of sales would you expect for a successful FTI inhibiitor, given that the cancer drug market is traditionally highly fragmented and the competition for FTI is considerable?

Given that ras is the oncogene most frequently found in human cancers 30% of most human cancers and at significantly higher rates in certain cancers including pancreatic (90%) and colon (50%), why hasn't Abbott targeted pancreatic cancer?

Is there more evidence implicationg Rho in place of Ras in the mechanism of cancer. Is Abbott working on the basic mechanism? Does Abbott feel it has proprietary mechanism knowledge that will aid drug design?

In the literature Merck has published several papers, but Abbott doesn't list them as having an active agent in clinical trials, Schering Plough's agent is the furthest along (in Phase III). Where is Merck today? What is its status today of Schering Plough's drug?

CONFIDENTIAL
property of John Hancock

Urokinase inhibitors

Potential interviewees for urokinase inhibitors

Ossowski L, Aguirre Ghiso J, Liu D, Yu W, Kovalski K
(strong *interview candidate*)
Department of Medicine, Mount Sinai School of Medicine, New York, NY, USA.
L.OSSOWSKI@SMTPLINK.MSSM.EDU

Kwaan HC, Wang J, Svoboda K, Declerck PJ
Department of Medicine, Northwestern University Medical School, Chicago, IL 60611, USA.
(*Possible for interview*)

Questions for interviewees on urokinase inhibitors

Notes on mechanism: urokinase activates plasminogen to plasmin which in turn breaks down basement membranes and interstitial matrix, which is required for solid tumor growth and metastasis. Disease-free survival (DFS) is related to levels of and interactions between (at least?) four components of the plasminogen activator system: urokinase-type plasminogen activator (uPA), its two inhibitors (PAI-1 and PAI-2), and its membrane receptor uPAR. Plasminogen activator inhibitor 1 (PAI-1) has been found to be a bad prognostic factor in a number of tumors but the reason has not been fully explained.

Since levels of components of the urokinase-type plasminogen activator (uPA) system of plasminogen activation are correlated with prognosis in several types of cancers, would this mean that each would make good treatment targets?

Are low or high levels of PAI-1 indicate poor prognosis. The abstract literature seems to indicate it is high levels. If it is high levels and PAI-1 is a urokinase inhibitor, what is the explanation? You would expect the opposite.

Since UPA initiates a cascade of proteolytic events that lead, are there any other steps in the cascade that would make for good targets? What are the best targets and why?

There are many approaches to cytostatic therapy, such as matrix metalloproteinase inhibitors, farnesyltransferase inhibitors, and tyrosine kinase inhibitors, serine protease inhibitors (e.g., urokinase inhibitors), endothelin ET-1 antagonists (bind to ETA receptors). Did I miss anything in this list(e.g., other approaches to angiogenesis inhibition)? Is there one approach that seems most promising? Least promising? How would you rank them? Is it too early to tell? Which

CONFIDENTIAL
property of John Hancock

are the most promising candidates within each approach?

One literature review indicated that approximately thirty cytostatic agents are in clinical trials to inhibit angiogenesis alone, and another fifty agents are in preclinical testing. Cytostatic drug development is a crowded field. Which of the large drug companies do you perceive as leaders in this area?

Questions for Abbott on urokinase inhibitors

Notes on mechanism: urokinase activate plasminogen to plasmin which in turn breaks down basement membranes and interstitial matrix, which is required for solid tumor growth and metastasis. Disease-free survival (DFS) is related to levels of and interactions between (at least?) four components of the plasminogen activator system: urokinase-type plasminogen activator (uPA), its two inhibitors (PAI-1 and PAI-2), and its membrane receptor uPAR. Plasminogen activator inhibitor 1 (PAI-1) has been found to be a bad prognostic factor in a number of tumors but the reason has not been fully explained.

Since levels of components of the urokinase-type plasminogen activator (uPA) system of plasminogen activation are correlated with prognosis in several types of cancers, would this mean that altering the levels of each would make good treatment targets?

Since UPA initiates a cascade of proteolytic events that lead to metastasis. Are there any other steps in the cascade that would make for good targets?) Why was urokinase chosen as the target? Because it initiates events in several different pathways?

CONFIDENTIAL
property of John Hancock

Selected Literature Abstracts

My comments are in *italics*.

Informative articles about cytostatic therapies in general

18: Cancer Res 1995 May 1;55(9):1856-62
Molecular insights into cancer invasion: strategies for prevention and intervention.
Kohn EC, Liotta LA, Laboratory of Pathology, National Cancer Institute, NIH, Bethesda, Maryland 28092, USA.
(*Liotta is a highly regarded cancer researcher. We should interview him or someone from his lab. Get suggestions on whom to interview from Carol Dahl. This particular article, however, is old.*)
The diagnosis and treatment of solid tumors usually begins at a late stage when most patients already have occult or overt metastasis. Many years of cancer progression precede diagnosis of most solid tumors. Novel noncytotoxic therapeutics may be specially suited for administration during this interval. An important window of intervention can be defined as the period during which transition from a hyperproliferative state to acquisition of the capacity for invasion and metastasis occurs. Investigation of the molecular basis of invasion is uncovering strategies for delaying progression of preinvasive carcinoma and treatment of primary tumors and established metastasis. Although tumor cell invasion might not be rate limiting for the growth of metastasis, anti-invasive agents can block tumor angiogenesis and thereby indirectly block metastasis growth. Two classes of molecular anti-invasion targets exist: (a) cell surface and extracellular proteins, which mediate sensing, adhesion, and proteolysis; and (b) signal transduction pathways, which regulate invasion, angiogenesis, and proliferation. Both categories of targets yield treatment approaches that are now being tested in the clinic. Metalloproteinase inhibitors, such as BB94, are based on the recognition that metalloproteinases play a necessary role in invasion and angiogenesis. (*Today–five years later–what is the status of BB94?*) The orally active signal transduction inhibitor carboxyamidotriazole modulates non-voltage-gated calcium influx-regulated signal pathways and reversibly inhibits tumor invasion, growth, and angiogenesis. Blockade of invasion, angiogenesis, or cellular signal pathways is likely to generate a cytostatic, rather than a cytotoxic effect. Cytostatic therapy constitutes an alternative paradigm for clinical translation that may complement conventional cytotoxic therapy. For patients with newly diagnosed solid tumors, long-term cytostatic therapy could potentially create a state of metastasis dormancy or delay the time to overt relapse following cytotoxic agent-induced remission. Clinical toxicity and pharmacology using oral cytostatic agents in phase I trials and in adjuvant settings will provide an important foundation for the translation of this approach to the preinvasive carcinoma period.
Publication Types:
Review
Review, tutorial

CONFIDENTIAL
property of John Hancock

PMID: 7728753, UI: 95246023

1: Oncologist 2000;5 Suppl 1:51-4
Clinical strategy for the development of angiogenesis inhibitors.
Carter SK
SUGEN, Inc., South San Francisco, California, USA. star-wescott@sugen.com
Angiogenesis inhibitors differ from conventional cytotoxic chemotherapy agents by targeting normal cells rather than tumor cells, which may contain multiple mutations. Because of this, the traditional strategy used in clinical development of cytotoxic agents may not be appropriate for these novel agents. Many clinical studies are now evaluating these agents with a new approach, referred to as the cytostatic paradigm. The cornerstone of the cytostatic paradigm is the use of time to progression (TTP) of disease as the decision-making criterion for "go/no go" in the early phases of clinical development. However, the use of TTP as the main criterion for clinical trials is complicated for a variety of reasons, including: A) the lack of standardized criteria accepted by regulatory authorities; B) the heterogeneity of the historical database, and C) the larger number of patients needed for the "go/no go" decision-making process. In addition, clinical trials of cytotoxic agents have traditionally used objective response (despite the controversy regarding objective response as a surrogate for clinical activity) as the main criterion for determining whether the results of phase II studies justify the pivotal phase III studies. Another aspect of the clinical development strategy is combining angiogenesis inhibitors with cytotoxic chemotherapy. The rationale for combination of angiogenesis inhibitors with cytotoxic agents is based on: A) different targets for these agents; B) lack of cross-resistance patterns; C) lack of myelosuppression with angiogenesis inhibitors allows administration of full doses of all agents, and D) the assumption that combining these agents will result in additive antitumor activity. Combination therapy with angiogenesis inhibitors may be attractive to both clinicians and their patients because it allows cytostatic agents to be used upfront in treatment while contributing to drug registration strategy (cytostatic/cytotoxic combination therapy versus cytotoxic therapy). The clinical development of the angiogenesis inhibitor SU5416, a small molecule inhibitor of vascular endothelial growth factor, is currently ongoing. In phase I trials, SU5416 demonstrated activity in both colorectal and non-small-cell lung cancer patients. Based on these encouraging results, phase III studies to evaluate combination of SU5416 with established cytotoxic therapy are planned. (***This competitive drug seems to be ahead of Abbott's candidates for NSCL***). These studies will include an interim analysis, the equivalent of a phase II evaluation of clinical activity. If successful, this strategic approach will save significant time in the clinical development process.
PMID: 10804092, UI: 20264300

2: Oncologist 2000;5 Suppl 1:20-7
Antiangiogenic strategies and agents in clinical trials.
Rosen L

CONFIDENTIAL
property of John Hancock

University of California Los Angeles School of Medicine, Los Angeles, California 10945, USA. LSROSEN@mednet.ucla.edu
The understanding that the growth of tumors depends on the acquisition of a blood supply has led to the development of new therapies for cancer and other angiogenic diseases based on inhibition of neovascularization. This review examines the role of angiogenesis in cancer progression and describes various strategies for interfering with this process. The developmental status of angiogenesis inhibitors in human clinical trials is presented, including their proposed mechanisms of action. (*This statement indicates this person should be interviewed, especially since this is a brand-new paper, but e-mail him to try to get a copy of the paper first.*) Standard chemotherapeutic agents and angiogenesis inhibitors are compared, noting that different end points might need to be considered in clinical trials and that drug resistance may be less of a problem with antiangiogenic therapy than with conventional chemotherapy regimens. The suggestion is made that cytotoxic chemotherapy and angiogenesis inhibitors used in combination may produce complementary therapeutic benefits in the treatment of cancer.
Publication Types:
Review
Review, tutorial
PMID: 10804087, UI: 20264295

13: Curr Pharm Des 2000 Mar;6(4):417-39
Angiogenesis: new targets for the development of anticancer chemotherapies.
Gourley M, Williamson JS
Department of Medicinal Chemistry, University of Mississippi, Mississippi, MS 38677, USA.
(*Perhaps the medicinal chemisitry perspective would be useful to us.*)
Angiogenesis is the process by which new blood vessels are formed from preexisting microvasculature. To ensure an adequate blood supply, tumor cells release angiogenic factors that are capable of promoting nearby blood vessels to extend vascular branches to the tumor. In addition, larger tumors have been shown to release angiogeneic inhibitory factors that prevent blood vessels from sending branches to smaller, more distant tumors that compete for oxygen and nutrients. Angiogenesis is a complex multistep biochemical process, and offers several potential molecular targets for non-cytotoxic anticancer therapies. Strategies for exploiting tumor angiogenesis for novel cancer drug discovery include: (i) inhibition of proteolytic enzymes that breakdown the extracellular matrix surrounding existing capillaries; (ii) inhibition of endothelial cell migration; (iii) inhibition of endothelial cell proliferation; (iv) enhancement of tumor endothelial cell apoptosis. There is also a host of miscellaneous agents that inhibit angiogenesis for which the specific mechanisms are not clear. Several methods have been developed for measuring antiangiogenic activity both in vitro and in vivo. Although there has been intensive research efforts focused at the phenomena of angiogenesis, as well as the search for antiangiogenic agents for more than two decades, many questions remain unanswered with regard to the overall biochemical mechanisms of the angiogenesis process and the potential

therapeutic utility of angiogenic inhibitors. Nevertheless potent angiogenic inhibitors capable of blocking tumor growth have been discovered, and appear to have potential for development into novel anticancer therapeutics. However there are still hurdles to be overcome before these inhibitors become mainstream therapies.

Publication Types:
Review
Review, academic
PMID: 10788590, UI: 20251313

CONFIDENTIAL
property of John Hancock

Sample articles on endothelin receptor antagonist field and advanced prostate cancer

My comments in *italics*.

6: Semin Oncol 1999 Apr;26(2):217-26
Drug development in prostate cancer.
Ripple GH, Wilding G
Department of Medicine, University of Wisconsin Comprehensive Cancer Center, Madison, USA.
Despite strategies aimed at early detection and treatment, prostate cancer remains a leading cause of morbidity and mortality among males. Current therapies have limited impact on the natural history of metastatic hormone-refractory prostate cancer (HRPC). With an improved understanding of tumor biology, including apoptosis, differentiation, cell cycling and signaling, and angiogenesis, many potential new targets for therapy have been unveiled. Modulation of these processes may result in cytotoxic or cytostatic effects. The evaluation of therapies based on manipulation of these targets may not be adequately addressed by current study designs and traditional parameters of efficacy. Examples of agents currently in clinical trials that illustrate some of the challenges presented to clinical investigators include monoterpenes such as perillyl alcohol (POH), vitamin D analogs, flavones such as flavopiridol, and angiogenesis inhibitors. Agents such as these are aimed at unique cellular targets and will require novel approaches to determine their clinical utility. Unfortunately, in the United States, only a small proportion of cancer patients, including prostate cancer patients, are enrolled in clinical trials. We must do better to efficiently assess promising new treatment approaches and improve outcome for our patients.
Publication Types:
Review
Review, tutorial
PMID: 10597732, UI: 20064602

11:Cancer Res 1996 Feb 15;56(4):663-8
Endothelin-1 production and decreased endothelin B receptor expression in advanced prostate cancer.
Nelson JB, Chan-Tack K, Hedican SP, Magnuson SR, Opgenorth TJ, Bova GS, Simons JW
James Buchanan Brady Urological Institute Research Laboratories, Johns Hopkins Hospital, Baltimore, Maryland 21287-2411, USA.
The potent vasoconstrictor endothelin-1 (ET-1) is at its highest concentration in the normal human ejaculate and is associated with the progression of metastatic prostate cancer. ET-1 protein expression is detected in situ in 14 of 14 primary cancers and 14 of 16 metastatic sites of human prostatic carcinoma. Exogenous ET-1 induces prostate cancer proliferation directly and enhances the mitogenic effects of insulin-like growth factor I, insulin-like growth factor II, platelet-derived growth factor, basic fibroblast growth factor, and epidermal growth factor in

CONFIDENTIAL
property of John Hancock

serum-free conditions in vitro. The ETA-selective receptor antagonist A-127722 (*an Abbott compound?*) inhibits ET-1-stimulated growth, but the ETB-selective receptor antagonist BQ-788 does not. ET-3, an ETB-selective agonist, also had no effect on prostate cancer growth. No specific ETB-binding sites could be demonstrated in any established human prostate cancer cell line tested, and ETB mRNA, detected by reverse transcription PCR, was reduced. The predominance of ETB binding on human benign prostatic epithelial tissue is not present in metastatic prostate cancer by autoradiography. In human prostate cancer progression to metastases, ET-1 and ETA expression are retained, whereas ETB receptor expression is reduced.
PMID: 8630991, UI: 96223664

6:Cancer Res 1998 Nov 1;58(21):4817-22
ET-1 expression and growth inhibition of prostate cancer cells: a retinoid target with novel specificity.
Hsu JY, Pfahl M
Sidney Kimmel Cancer Center, San Diego, California 92121, USA.
Endothelin-1 (ET-1) is not only a potent vasoconstrictor but also serves as an important growth stimulator in various cancers, including breast, cervical, pancreatic, and prostate cancer. This suggests that blockage of ET-1 production may suppress tumor growth and possibly metastasis. We observed that certain synthetic retinoids, and all-trans-retinoic acid can repress LNCaP prostate cancer cell growth in vitro. In addition, these retinoid compounds counteracted exogenous ET-1-induced growth stimulation. Retinoid-dependent growth retardation of LNCaP cells coincided with suppression of ET-1 gene expression to a level undetectable by reverse transcription-PCR. (How do *the small-molecule retenoid drugs suppress ET-1 gene expression (affect promotor activity, see below)? Is ABT-627 a retenoid compound which works at the level of transscrition, or is a traditional antagonist binding directly to the Eta receptor? Do retenoids represent serius competition to ABT-627? Are they in development and by whom?*) Contrarily, the androgen-insensitive DU145 cells were refractory to retinoid treatment. To investigate the underlying mechanisms of the cell-specific response to retinoids, we transfected ET-1 promoter constructs containing wild-type or mutated AP-1 or GATA-2 site into prostate cancer cells. Distinct regulations of ET-1 promoter activity were found; in LNCaP cells, both binding sites are essential for optimal promoter activation, whereas in DU145 cells, additional promoter sequences and/or transcriptional factors seem to be involved. Furthermore, several anti-AP-1 selective retinoids failed to repress ET-1 promoter activity and to exhibit a cell growth-inhibitory effect on LNCaP cells, suggesting that different retinoid structural configurations are required for the inhibition of an AP-1 complex versus an AP-1/GATA-2 complex.
PMID: 9809984, UI: 99025856

7:Ned Tijdschr Geneeskd 1997 Sep 20;141(38):1806-10
[Endothelins: possibly a new pharmacological approach in cardiovascular diseases, kidney diseases and oncological disorders].
[Article in Dutch]

CONFIDENTIAL
property of John Hancock

Kroodsma JM, Rabelink AJ
Academisch Ziekenhuis, afd. Nefrologie, Utrecht.
Only 10 years ago, the vasoconstricting peptide endothelin was discovered; it is produced by endothelial cells. Different isoforms and receptors of endothelin have been identified. The effects of endothelin-I, the most important isoform, are mainly vasoconstriction and proliferation of cells. (*ET-1 is the most important ET isoform*) In the last few years endothelin receptor antagonists have become available, which can delineate the clinical importance of the endothelin system. Possible indications for endothelin receptor blockers are renal disease (acute and chronic renal failure) and cardiovascular disease (heart failure; restenosis after percutaneous transluminal coronary angioplasty (PTCA); pulmonary hypertension; systemic hypertension). There is also a possible role for endothelin receptor blockers in oncology (prostatic carcinoma). (*This 1997 paper talks about possible roles of Eta blockers in prostate cancer.*) Currently clinical trials are being carried out to determine the efficacy of these compounds for the above-mentioned indications. (*Do these authors know of other clinical trials in progress?*)
Publication Types:
Review
Review, tutorial
PMID: 9545734, UI: 98207344

<u>Sample articles on matrix metalloproteinase inhibitors</u>

1: Drugs 2000 May;59(5):1043-55
Clinical potential of matrix metalloprotease inhibitors in cancer therapy.
Heath EI, Grochow LB, Division of Medical Oncology, Johns Hopkins Oncology Center, Baltimore, Maryland 21231, USA. heathel@jhmi.edu
(*These authors would be good for an interview* on MMPI's)
[Medline record in process]
Matrix metalloproteases (MMP) are a family of enzymes that contribute to the degradation of the extracellular matrix. The destruction of the extracellular matrix eventually leads to tumour invasion, metastasis and angiogenesis. Realising this mechanism of action, there is tremendous potential for inhibitors of MMP in cancer therapy. Extensive preclinical data have shown that administration of matrix metalloprotease inhibitors (MMPI) to different animal models results in a reduction in primary tumour growth as well as in the number and size of metastatic lesions. Based on promising preclinical studies, synthetic MMPI have been developed and taken into clinical trials. These include marimastat, BAY- 129566, CGS-27023A, prinomastat (AG-3340), BMS-275291 and metastat (COL-3). These drugs are all in different stages of clinical development, ranging from phase I to III. In general, musculoskeletal problems, such as joint stiffness and pain in hands, arms and shoulders seem to affect most patients in varying degrees, depending on the dose and type of compound administered. (*Depending on the level of pain,*

CONFIDENTIAL
property of John Hancock

could reduction in quality of life outweigh the value of delaying progression?) In addition to single agent therapy, several MMPI have entered trials of combination therapy. The objective of combining chemotherapy with an MMPI is to potentiate tumour cytotoxicity as well as to reduce the size and number of metastatic lesions. Several compounds have entered phase III combination therapy trials, but it is still too early to report any data. (*Any data since this article was written.*) There is ongoing research in correlating biological endpoints, such as levels of MMP and markers of angiogenesis with clinical response. As the field of MMP and their inhibitors continues to mature, its role in cancer therapeutics will be better defined. PMID: 10852638, UI: 20309478

1: Invest New Drugs 1999;17(4):387-99
Matrix metalloproteinase inhibitors: applications in oncology.
Yip D, Ahmad A, Karapetis CS, Hawkins CA, Harper PG, Department of Medical Oncology, Guy's Hospital, London, United Kingdom.
Matrix metalloproteinases (MMP) are a group of zinc dependent enzymes which include the interstitial collagenases, stromelysins, gelatinases and membrane-type metalloproteinases. They are involved in the remodelling and turnover of the extracellular matrix proteins. They play a role in wound healing and the pathogenesis of arthritis. In malignancies they play a role in tumor invasion, metastasis and angiogenesis. A number of synthetic matrix metalloproteinase inhibitors (MMPIs) have been developed for clinical use. In preclinical tumor models they have shown promising activity in achieving inhibition of MMPs and reducing tumor growth and metastatic spread. Some have also shown additive or synergistic effects with cytotoxic agents. Phase I and II studies in human subjects have defined the main side effects of these agents as being musculoskeletal pains or arthralgias. As they are cytostatic agents rather than cytotoxic in activity conventional measurements of radiological response for assessment are not applicable in trials. Biological activity has been demonstrated in certain cancers by the effects on levels of tumor markers as surrogate markers of tumor response and also by a fibrotic stromal reaction seen in tumor tissue. Newer agents have been developed with selective inhibition of certain MMPs in an attempt to reduce the side effects. A number of phase III human clinical trials evaluating MMPs are being carried out at present but only one has been formally reported so far. This study suggested that marimastat had no survival advantage when compared to chemotherapy with gemcitabine in advanced pancreatic carcinoma. Current trials are assessing efficacy of MMPIs in maintenance of remission after other modalities of therapy or in combination with cytotoxic agents. (*With no survival advantage, would the FDA be skeptical about slower progression of the disease, especially since there are side effects. To play devil's advocate, you could argue you are not prolonging the patient's life and at the same time you are inflicting pain?*) MMPs have also been demonstrated to play an important role in the articular cartilage destruction seen in both rheumatoid arthritis and osteoarthritis. The use of MMPIs in both ex vivo and in vivo models have shown promising results and trials are in process to assess their potential role in the control of articular destruction. The true therapeutic role of MMPIs

await the results of these randomized studies. (What is the extent of Hancock's right to ABT-518?)
Publication Types:
Review
Review, tutorial
PMID: 10759405, UI: 20221159

5: Breast Cancer Res Treat 1998;52(1-3):125-36
Matrix metalloproteinase inhibitors.
Brown PD, Department of Clinical Research, British Biotech Pharmaceuticals Ltd, Oxford, UK.
(*This company is the developer of Marimistat, the Abbott Phase III competitor.*)
Matrix metalloproteinases (MMPs) are a family of enzymes responsible for the breakdown of proteins of connective tissue. Through this action they play an important role in growth, development and tissue repair. Recent studies also suggest that MMPs are utilised in cancer, facilitating both local tumour invasion and metastasis. Levels of certain MMPs such as stromelysin-3 and gelatinase are elevated in tumour-associated stroma compared to non-involved tissue. (*Does the mention of gelatinase here mean that British Biotech is also working on gelatinase inhibitors? What does Marimistat target?*) A series of synthetic low molecular weight MMP inhibitors have been produced. Early inhibitors were based on the peptide structure of collagen, although more recently non-peptide inhibitors have also been developed. The inhibitors are selective for the MMP family and are active at low nanomolar concentrations. Experiments in models of breast cancer have shown that MMP inhibitors can significantly reduce the growth rate of both primary and secondary tumours, and can block the process of metastasis. Several MMP inhibitors have now started clinical trials in patients with advanced malignancy. Although not the optimum setting for a tumouristatic agent, early results suggest this approach may be effective in slowing tumour growth. Trials in the adjuvant setting will provide the most important test of these inhibitors and should determine their potential to complement existing cytoreductive treatments and prolong survival.
Publication Types:
Review
Review, tutorial
PMID: 10066077, UI: 99163960

7: Drugs R D 1999 Feb;1(2):117-29
Clinical potential of matrix metalloprotease inhibitors.
Wojtowicz-Praga S
Theradex, Princeton Junction, New Jersey, USA.
(*If this drug company is not a drug company, these authors may be good interview candidates? I should internet search this company.*)
The mature extracellular matrix (ECM) is a heterogenous substance produced by a variety of

cells, mostly of mesothelial origin. The ECM serves as a tissue skeleton, a medium of communication between cells and as a barrier between the cells and the vascular system. The matrix is continuously remodelled in the living tissues. A variety of proteases, including matrix metalloproteases (MMPs), contribute to matrix destruction. These proteases are neutralised by naturally occurring inhibitors such as alpha 2-macroglobulin or tissue inhibitors of metalloproteases (TIMPs). Proteases and their inhibitors are often produced by the same cells, thus matrix remodelling is localised and strictly controlled. The MMPs are zinc-endopeptidases functioning at a neutral pH and requiring ionised calcium for activity. The extracellular matrix is an essential part of every organ and tissue type. MMPs are the key components of the system that dynamically controls the structure and function of the ECM. MMPs have been implicated in corneal disease, periodontal disease, dermatological disorders, atherosclerosis, bone and joint disorders, fibrotic disease, vascular abnormalities, malignancy and many other pathological processes. Several synthetic inhibitors of MMPs have been developed and many of them are currently in clinical trials. Compounds discussed in this article include batismastat, marimastat, BAY12-9566, AG-3340, OPB-3206, KBR-7785, KBR-8301, CDP-845 (CT-1746), metastat and AE-941 (Neovastat). (*They seem to be knowledgable about a number of compounds.*)
Publication Types:
Review
Review, tutorial
PMID: 10566004, UI: 20032438

<u>Sample articles on farnesyltransferase inhibitors</u>

1: Eur J Cancer 1999 Sep;35(9):1394-401
Effect of novel CAAX peptidomimetic farnesyltransferase inhibitor on angiogenesis in vitro and in vivo.

Gu WZ, Tahir SK, Wang YC, Zhang HC, Cherian SP, O'Connor S, Leal JA, Rosenberg SH, Ng SC. Abbott Laboratories, Department 4N6 AP9/2, Abbott Park, Illinois, USA.

Ras oncogenes can contribute to tumour development by stimulating vascular endothelial growth factor (VEGF)-dependent angiogenesis. The effect of Ras on angiogenesis may be affected by farnesyltransferase inhibitors (FTI) since farnesylation of Ras is required for its biological activity. In this paper we evaluated the effect of A-170634, a novel and potent CAAX FTI on angiogenesis. (*This is not the one that Abbott abandoned which was ABT 839. What is the status of this one? Which inhibitors does Abbott have the rights to?*) Human umbilical vein endothelial cell (HUVEC) tube formation and VEGF secretion were used to assess the effect of A-170634 on angiogenesis in vitro. In vivo, nude mice were injected with the K-ras mutant colon carcinoma cell line HCT116 and treated subcutaneously with A-170634 using osmotic minipump infusion for 10 days. The effect of A-170634 on corneal angiogenesis in vivo was

assessed using pellets containing hydron, VEGF, A-170634 or vehicle. In vitro, A-170634 selectively inhibited farnesyltransferase activity over the closely related geranylgeranyltransferase I, inhibited Ras processing, blocked anchorage-dependent and -independent growth of HCT116 K-ras mutated cells, decreased HUVEC capillary structure formation, decreased VEGF secretion from tumour cells and HUVEC growth stimulating activity in a dose-dependent manner. In vivo, tumour growth was decreased by 30% and vascularisation in and around the tumours was reduced by 41% following drug-treatment with no apparent toxicity to the animals. VEGF-induced corneal neovascularisation was reduced by 80% following A-170634 treatment for 7 days. The data presented here demonstrated that A-170634 was a potent and selective peptidomimetic CAAX FTI with anti-angiogenic properties. (*Are all Abbott's inhibitors peptidomimetics? What is their estimated molecular weight and production cost?*) These results implied that A-170634 may affect tumour growth in vivo by one or more antitumour pathways. PMID: 10658533, UI: 20123003

5: Oncogene 1998 Sep 17;17(11 Reviews):1439-45
Non-Ras targets of farnesyltransferase inhibitors: focus on Rho.
Lebowitz PF, Prendergast GC
(*a good interview candidate, but Prendergast is with DuPont. Maybe interview Lebowitz.*)
The Wistar Institute, Philadelphia, Pennsylvania 19104, USA.
Farnesyltransferase inhibitors (FTIs) are a novel class of cancer therapeutics whose development was based on the discovery that the function of oncogenic Ras depends upon its posttranslational farnesylation. Significantly, experiments in animal models have shown that FTIs have promise as nontoxic cancer therapeutics. However, cell biological studies have suggested that FTIs may act at a level beyond that of suppressing Ras function, so the exact mechanism of action has emerged as a question of major interest. Here, we review evidence that proteins other than Ras are important targets for inhibition, summarize findings suggesting a role for farnesylated Rho proteins prompted by studies on RhoB, and suggest a new model for how FTIs exert their biological effects. The 'FTI-Rho hypothesis' proposes that FTIs act in part by altering Rho-dependent cell adhesion signals which are linked to pathways controlling cell cycle and cell survival and which are subverted or defective in neoplastic cells. This model offers a novel framework for addressing the questions about FTI biology, including the basis for lack of toxicity to normal cells, cytotoxic versus cytostatic effects on tumor cells, and the persistence and drug resistance of malignant cells in FTI-treated animals. (*Lack of toxicity to normal cells is significant. Does this potentially make FTI's potentially much better than MMPI's?*)
Publication Types:
Review
Review, tutorial
PMID: 9779989, UI: 98451269

Rowinsky EK, Windle JJ, Von Hoff DD

CONFIDENTIAL
property of John Hancock

(*good interview candidate*)
Institute for Drug Development, Cancer Therapy and Research Center, San Antonio, TX 78229-3272, USA. erowinski@saci.org
Ras proteins are guanine nucleotide-binding proteins that play pivotal roles in the control of normal and transformed cell growth and are among the most intensively studied proteins of the past decade. After stimulation by various growth factors and cytokines, Ras activates several downstream effectors, including the Raf-1/mitogen-activated protein kinase pathway and the Rac/Rho pathway. In approximately 30% of human cancers, including a substantial proportion of pancreatic and colon adenocarcinomas, mutated ras genes produce mutated proteins that remain locked in an active state, thereby relaying uncontrolled proliferative signals. Ras undergoes several posttranslational modifications that facilitate its attachment to the inner surface of the plasma membrane. The first-and most critical-modification is the addition of a farnesyl isoprenoid moiety in a reaction catalyzed by the enzyme protein farnesyltransferase (FTase). It follows that inhibiting FTase would prevent Ras from maturing into its biologically active form, and FTase is of considerable interest as a potential therapeutic target. Different classes of Ftase inhibitors have been identified that block farnesylation of Ras, reverse Ras-mediated cell transformation in human cell lines, and inhibit the growth of human tumor cells in nude mice. In transgenic mice with established tumors, Ftase inhibitors cause regression in some tumors, which appears to be mediated through both apoptosis and cell cycle regulation. FTase inhibitors have been well tolerated in animal studies and do not produce the generalized cytotoxic effects in normal tissues that are a major limitation of most conventional anticancer agents. There are ongoing clinical evaluations of FTase inhibitors to determine the feasibility of administering them on dose schedules like those that portend optimal therapeutic indices in preclinical studies. Because of the unique biologic aspects of FTase, designing disease-directed phase II and III evaluations of their effectiveness presents formidable challenges. Publication Types:
Review
Review, tutorial
PMID: 10550163, UI: 20018280

<u>Sample articles on urokinase inhibitors</u>

1: Am Surg 2000 May;66(5):460-4
Suppression of the invasive capacity of human breast cancer cells by inhibition of urokinase plasminogen activator via amiloride and B428.
Evans DM, Sloan-Stakleff K., Calhoun Research Laboratory, Akron General Medical Systems, Ohio 44307, USA.

Inhibition of urokinase plasminogen activator (uPA) has been shown to suppress cancer cell invasion and metastasis in the laboratory setting by numerous investigators. (This year 2000 assessment agrees with Abbott's assessment, that all are preclinical.) Most studies have used murine cell lines implanted in syngeneic rodents or transfected human cell lines grown in

immunocompromised laboratory hosts. In this study using Matrigel invasion chambers and two separate uPA inhibitors, amiloride and B428, the invasive capacity of unaltered human breast cancer cells was significantly suppressed. Cell proliferation was also suppressed to a lesser degree. These findings suggest that uPA inhibition may be a valid clinical approach to the control of the invasion and metastasis of human cancers.
PMID: 10824746, UI: 20282860

2: Vestn Ross Akad Med Nauk 1999;(8):58-61
[The clinical prospects for the study of the plasminogen activation system in breast cancer].
[Article in Russian]
Gershtein ES, Kushlinskii NE
Urokinase-type plasminogen activator (UPA) which is a serine protease may play a key role in the processes of tumor invasion and metastasis since it converts plasminogen to plasmin and initiates a cascade of proteolytic events that lead to the degradation of extracellular matrix. (Are there any another steps in the cascade that would make for good targets?) Experiments have demonstrated that some other components, except UPA itself, can be very important in this process, including UPA receptor (UPAR) and UPA inhibitors PAI-1 and PAI-2. All these proteins are present either in the tumor cells or in the tumor-infiltrating macrophages and stromal elements, and by acting in concert, they provide a feed-back-regulated mechanism of plasmin activation and amplification. Clinical retrospective studies using predominantly ELISA techniques have shown that the high levels of UPA, PAI-1 and UPAR in the tumor tissue are associated with poor prognosis both for overall and for disease-free survival of breast cancer patients, and the elevated level of PAI-2 may be indicative of better survival. UPA and PAI-1 are now regarded as rather potent independent predictors in breast cancer. Further clinical prospects of investigations and application of the components of the plasminogen activation system are discussed. Publication Types:
Review
Review, tutorial

KLOTZ DEPOSITION EXHIBIT 11

D'S EXHIBIT 556

From: Lynn C. Klotz [LynnKlotz@compuserve.com]
Sent: Tuesday, July 11, 2000 10:17 AM
To: Blewitt, Stephen
Subject: Rest of research summaries

Steve,

I am back in town.

Attached to this fax are summaries of literature searches and questions for:

** ABT-980 (BPH)
** A-254751 (cancer, cytotoxic drug)
** ABT-594 (neuropathic pain)

I think now you have a complete set of summaries. If you are missing something, let me know as they are all done.

For ABT-980, there are really no surprises. Of course, there are always some questions.

For A-254751 and ABT-594 there are questions, in my mind, about whether they will complete clinical trials. This makes it even more important that we see a summary of the latest clinical trial data.

Let's discuss when you have time.

I am in the process of getting contact information for the interviews. I hope to have my assistant do this in the next few days. Then I will start interviewing, after I look over the questions one more time.

- Lynn

Abbott's Neuropathic Pain Agonist (ABT-594)

file: abbott-neuropathic

Potential interviewee's for ABT-594

No potential interviewees yet identified, I will search MedLine under "neuropathic pain AND therapy."

Questions for experts on neuropathic pain

There are a number of adjuvant analgesics in clinical development that could compete with nicotinic acetylcholine receptor agonists. Some examples are pregabalin (Parke-Davis) in Phase III trials, GV196771 (Glaxo) in Phase II, mamantine (Merz) in Phase II, which of these--or others that you know of--show special promise for neuropathic pain?

A variety of nicotinic acetylcholine receptor agonists such as nicotine, epibatidine and the azetidinyl ether, (R)-5-(2-azetidinylmethoxy-2-chloropyridine (ABT-594) appear to possesses significant efficacy in preclinical models of pain. Are any of these in clinical trials? Are any especially promising? How do nicotinic acetylcholine receptor agonists stack up against the other kinds of drug candidates (above)?

It has been reported that some of the nicotinic acetylcholine receptor agonists have a small therapeutic window, which I'll define here as:

(conc. for intolerable side effects)/(conc. for efficacy)

What is an acceptable therapeutic window for pain relievers in general, neuropathic pain relievers?
It seems to me that for pain relievers, where a patient might take many more pills than recommended, a therapeutic window of two to three is not sufficient? Comment. What size of therapeutic window does the FDA look for in pain medications?

Questions for Abbott on ABT-594 and its competition

Page 3 in the Abbott report is blank. This is a real page, not just a faxing error, as the next readable page is 4. Was it eliminated for confidentiality reasons?

According to one of your own publications, a variety of nicotinic acetylcholine receptor agonists such as nicotine, epibatidine and the azetidinyl ether, (R)-5-(2-azetidinylmethoxy-2-chloropyridine (ABT-594) possesses significant efficacy in preclinical models of pain. You do not list any of these as being in clinical trials. Will any enter trials? Do you see any as competitors?

It has been reported that some of the nicotinic acetylcholine receptor agonists have a small therapeutic window, which I'll define here as:

(conc. for intolerable side effects)/(conc. for efficacy)

What is an acceptable therapeutic window for pain relievers in general, neuropathic pain releivers? Is there something about diabetic pain that would allow for a small therapeutic window? ABT-594 appears to have a therapeutic window of only two to three (Abbott memorandum p.5). It seems to me that for pain relievers, where patients might take many more pills than recommended, a therapeutic window of two to three is not sufficient? Comment. (Abbott is in Phase IIb clinical trials, which is an indicator of safety but not therapeutic window.) What size of therapeutic window does the FDA look for in pain medications?

A Merck study claims that in rats "ABT-594 did not cause rotarod impairment at antinociceptive doses but did cause hypothermia and life-threatening adverse effects including seizures." This study also says its results suggest "ABT-594 has nicotine-like dependence liability....These findings indicate that the acute safety profile of ABT-594 is not significantly improved over other nicotinic analgesics." Also, Novartis finds in rats that "ABT-594 dose-dependently increased tail flick latencies but only at doses that also disrupted performance in the rotarod test" What does Abbott have to say about these conclusions which indicate (significant?) side-effects atconcentrations of use?

It should be noted that animal studies are all studies of nociceptive pain (caused by injuious stimuli, eg. heat) as opposed to neuropathic pain (caused by never injury). Are there often differences in the effects of anlagesics in the two tests? Are there any animal tests to measure effects on neuropathic pain?

Novartis also claims "In all tests, (+)-epibatidine was significantly more potent than ABT-594." According to Abbott, ABT-594 is as efficacious as (+)-epibatidine, which is too toxic for use .)

<u>Example abstracts</u>

1: Pain 2000 Apr;85(3):443-50
Analgesic and toxic effects of ABT-594 resemble epibatidine and nicotine in rats.
Boyce S, Webb JK, Shepheard SL, Russell MG, Hill RG, Rupniak NM
Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, UK. susan_boyce@merck.com
(*Why is Merck publishing on an Abbott drug?*)
The present study directly compared the antinociceptive and toxic effects of the neuronal nicotinic receptor agonist ABT-594(*It is an agonist, not an antagonist*) ((R)-5-(2-azetidinylmethoxy)-2-chloropyridine) with (-)-nicotine and (+)-epibatidine. Like (-)-nicotine (0.8 and 1.6 mg/kg s.c.) and (+)-epibatidine (0.005 and 0.01 mg/kg s.c.), ABT-594 (0.05 and 0.1 mg/kg s.c.) increased response latencies in the hot-plate test in rats, indicating that it has antinociceptive activity. In contrast to (-)-nicotine and (+)-epibatidine, ABT-594 did not

cause rotarod impairment at antinociceptive doses but did cause hypothermia and life-threatening adverse effects including seizures. (*Merck claims ABT-594 causes life-threatening seizures in rats. What is Abbott'r response?*) ABT-594 (0.01 and 0.1 mg/kg i.v.) also produced a dose-dependent increase in blood pressure resembling that observed with (-)-nicotine (0.03, 0.1 and 0. 03 mg/kg i.v.) and (+)-epibatidine (0.001 and 0.003 mg/kg i.v.). Both the antinociceptive and toxic effects (convulsions and hypertension) were abolished by pretreatment with the brain penetrant neuronal nAChR antagonist mecamylamine (1 mg/kg s.c.; i.v. for cardiovascular studies), demonstrating that these actions of ABT-594 were mediated via activation of neuronal nicotinic receptors. Continuous infusion of ABT-594 (0.2 mg/kg per day s.c.) to rats for 7 days followed by challenge with mecamylamine (1 mg/kg i.p.) induced a nicotine-like abstinence syndrome suggesting that ABT-594 has nicotine-like dependence liability. These findings indicate that the acute safety profile of ABT-594 is not significantly improved over other nicotinic analgesics. (*"other nicotinic analgesics" indicates that ABT-594 is not alone. Are others on the market?*) (*What does Merck have to say about these conclusions? It should be noted that this is a study of nociceptive pain (caused by injuious stimuli, elg. heat) as opposed to neuropathic pain(caused by never injury).*)
PMID: 10781917, UI: 20245628

4: Biochem Pharmacol 1999 Sep 15;58(6):917-23
Therapeutic potential of neuronal nicotinic acetylcholine receptor agonists as novel analgesics.
(*Abbott calls these novel analgesics; in contrast to the Merck article which states "acute safety profile of ABT-594 is not significantly improved over other nicotinic analgesics."*)
Decker MW, Meyer MD
Neurological and Urological Diseases Research, Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL 60064-6125, USA. michael.decker@abbott.com
Pharmacological treatments for pain have come largely from two classes of compounds--the opioids and the nonsteroidal anti-inflammatory drugs (NSAIDs). Because of deficiencies associated with these two classes of compounds, exploration of novel approaches to pain relief has intensified of late. Nicotine, a neuronal nicotinic acetylcholine receptor (nAChR) agonist, has long been known to have antinociceptive effects in both experimental animals and humans. The relatively modest antinociceptive effects and the toxicities associated with nicotine preclude its development as an analgesic agent. However, recent discoveries in the nAChR field have stimulated interest in nAChR-targeted compounds as potential analgesic agents. Epibatidine, a potent nAChR agonist, was found to have full efficacy relative to opioids in preclinical pain models. Although epibatidine is toxic, these observations demonstrated that modest efficacy is not a general limitation of nAChR agonists. Moreover, exploration of the molecular biology of nAChRs revealed evidence of receptor diversity, suggesting that nAChR subtype-selective agents less toxic than nicotine might be discovered; and early medicinal chemistry efforts already have resulted in compounds with improved safety profiles. For example, ABT-594 is a nAChR agonist with the antinociceptive efficacy of epibatidine, but with an improved safety profile.(*With a therapeutic window of only 2,[Abbott memorandum p.----), is the saftey profile improved enough for FDA approval? Abbott is in Phase IIb, which is an indicator of safety. For pain relievers, which might be abused by people in pain, is a therapeutic window of 2 enough?*) This commentary reviews recent findings with nAChR-targeted compounds, explores potential mechanisms responsible for nAChR-mediated antinociception, and raises issues that must be

addressed in developing compounds of this class as analgesics.
Publication Types:
Review
Review, tutorial
PMID: 10509744, UI: 99437443

Abbott's Benign Prostatic Hyperplasia Drug (ABT-980)

file: abbott-bph (abbott-b.wpd)

<u>Potential interviewee's for ABT-980</u>

Alpha-adrenoceptor antagonists in the treatment of benign prostatic hyperplasia.
Cooper KL, McKiernan JM, Kaplan SA
Department of Urology, College of Physicians and Surgeons, Columbia University, New York, New York, USA.
(*potential interview candidates*)

Beduschi MC, Beduschi R, Oesterling JE
Section of Urology, University of Michigan, Ann Arbor, USA.
(*Good interview candidates*)

Lepor H
Department of Urology, New York University Medical Center, New York 10016, USA.
(*possible interview candidate, but may be working with company marketing tamsulosin*)

<u>Questions for experts in BPH</u>

Note to help orient discussion: "The development of alpha-adrenergic blocking agents, [has proceeded] from nonselective alpha-antagonists, to selective alpha1-antagonists, to the more selective alpha1A-antagonists. It is anticipated that more specific agents will optimize the therapeutic effectiveness of alpha-adrenergic blockade in the prostate while reducing the side effects associated with alpha-adrenergic blockade in other areas of the body, such as the vascular system."

Recently, efforts have focused on use of alpha1A-urospecific antagonists such as tamsulosin, alfuzosin, and Abbott-980 in an attempt to achieve similar clinical results as doxazosin and terazosin without systemic adverse effects. Are these alpha1A selective drugs expected to be significantly superior to the older drugs? Why? Are all these drugs structurally different and what is the implication regarding toxicity, potency and pharmacokinetics?

How significant a difference is there in urinary flow rates between the older drugs terazosin, finasteride, etc. and the new selective drugs like Tamsulosin. If there is not much difference, why is Tamsulosin use increasing so rapidly? Is it because there is a significant difference of adverse effects with the selective alpha1a-adrenoceptor antagonists?

One review article states "controversy remains as to whether prostatic smooth muscle contraction is mediated by the alpha1A-adrenoceptor, or by another novel alpha1-adrenoceptor subtype (not corresponding to any of the three known recombinant alpha1-adrenoceptors)." This

indicates there could be a better target, as yet undiscovered. What is your view on this?

One literature study refers to a patient population that is responsive to alpha1-adrenoceptor antagonists. Does this mean there is a subgroup of patients that don't respond to BPH drugs targeted to alpha1-adrenoceptor? How big is this subgroup?

How would you compare the drugs in clinical trials Dutasteride, Xatra (alfuzosin), HP-4, ABT-980, KMD-3213? Which is most promising? Least promising? Why? Am I missing any promising ones.

Yamanouchi/Glaxo's Phase III drug duasteride is a 5alpha-reductase inhibitor. What are the advantages/disadvantages of this target versus alpha1A-adrenoceptor targeted drugs? Could one advantage be that there are less enzyme targets than membrane receptor targets, so that an enzyme inhibitor could be used in much lesser concentrations?

Questions for Abbott on ABT-980 and competition

In a Chinese literature study comparing a selective (tamsulosin) and non-selective (terazosin) alpha 1-adrenoceptor antagonists, Tamsulosin showed better results in maximum urinary flow rate (Qmax), and average urinary flow rate (AFR). But the results, in my opinion, were not dramatically different. What are Abbott's comparative results between uroselective ABT 980 and non uroselective drugs?

How significant a difference is there in urinary flow rates between the older drugs terazosin, finasteride, etc. and the new selective drugs like Tamsulosin. If there is not much difference why is Tamsulosin use increasing so rapidly? Is it because there is a significant difference of adverse effects with the selective alpha1-adrenoceptor antagonists? What is the adverse effect profile for ABT-980 compared with competitors?

One literature study refers to a patient population that is responsive to alpha1-adrenoceptor antagonists. Does this mean there is a subgroup of patients that don't respond to BPH drugs targeted to alpha1-adrenoceptor? How big is this subgroup?

One review article states "controversy remains as to whether prostatic smooth muscle contraction is mediated by the alpha1A-adrenoceptor, or by another novel alpha1-adrenoceptor subtype (not corresponding to any of the three known recombinant alpha1-adrenoceptors)." This indicates there could be a better target, as yet undiscovered.

Another 1999 review states, "long term studies must be done to determine whether pharmacological uroselectivity is actually clinically relevant." What is the meaning of this cautionary note?

Is Tamsulosin (Flomax) a Merck drug? If not does Merck have a drug for BPH in clinical trials?

CONFIDENTIAL
JH 003020

Is Abbott aware of KMD-3213, the Kissei Pharmaceutical Co drug? They claim it is more uroselective and longer lasting than tamsolusin.

Like Abbott's 980, both Tamsulosin and Alfuzosin (Xatral) which is Synthelabo's drug in Phase II trials, are also alpha1A-urospecific antagonists. What are the advantages, disadvantages with respect to ABT-980? Is the main advantage the 156/1 1a vs 1b receptor selectivity ratio? How does this selectivity reflect itself at the patient level? Is Abbott 980, structurally different enough, so there will be no patent issues?

Additionally, Yamanouchi/Glaxo's Phase III drug duasteride is a 5alpha-reductase inhibitor. What are the advantages/disadvantages of this target?

<u>Example articles</u>

Drugs 1999 Jan;57(1):9-17
Alpha-adrenoceptor antagonists in the treatment of benign prostatic hyperplasia.
Cooper KL, McKiernan JM, Kaplan SA
Department of Urology, College of Physicians and Surgeons, Columbia University, New York, New York, USA.
(potential interview candidates)
Lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH) have a significant impact on the lifestyle of older men. Transurethral resection of the prostate (TURP) is the most effective surgical therapy for this condition but an increasing number of patients are electing conservative medical therapy. Alpha-Adrenoceptor antagonists and 5alpha-reductase inhibitors are the 2 categories of drug therapy currently available for BPH. *(Yamanouchi/Glaxo's Phase III drug duasteride is a 5-alpha drug. What are the advantages/disadvantages of this target?* Use of alpha-adrenoceptor antagonists in the treatment of BPH is based on their ability to prevent the neural stimulation which induces prostate smooth muscle contraction, producing lower urinary tract symptoms. Several studies have demonstrated that alpha-receptors predominate in the prostatic stroma, capsule and bladder neck. Initial work focused on the use of phenoxybenzamine, a nonspecific alpha-blocker, in the treatment of BPH. While results were promising, significant adverse effects and concern over potential mutagenicity have resulted in a lack of use of this medication for this indication. Subsequent attention was directed towards the short-acting alpha-specific antagonist prazosin. Results conflicted regarding whether an actual sustained improvement in lower urinary tract symptoms could be achieved with this medication, and because of twice daily dosing compliance issues were a drawback. Thus, the mainstay in pharmacological treatment of BPH over the past decade has been 2 once-a-day alpha-specific antagonists, doxazosin and terazosin. Over 75% of all prescriptions written for BPH are for one of these 2 medications. Despite their tremendous success in both decreasing urinary symptoms and increasing urinary flow rates, systemic adverse effects can be bothersome. Recently, efforts have focused on use of alpha1A-urospecific antagonists such as tamsulosin and alfuzosin in an attempt to achieve similar clinical results as doxazosin and terazosin without systemic adverse effects. *(Alfuzosin (Xatral) is Synthelabo's drug in Phase II. What are its advantages, disadvantages with respect to ABT-980?*) Thus far, results are promising, but long term studies

must be done to determine whether pharmacological uroselectivity is actually clinically relevant.
(What is the meaning of this cautionary note?)
Publication Types:
Review
Review, tutorial
PMID: 9951948, UI: 99135419

9: Urology 1998 Jun;51(6):861-72
Alpha-blockade therapy for benign prostatic hyperplasia: from a nonselective to a more selective alpha1A-adrenergic antagonist.
Beduschi MC, Beduschi R, Oesterling JE
Section of Urology, University of Michigan, Ann Arbor, USA.
(*Good interview candidates*)
Benign prostatic hyperplasia (BPH) is very common in older men, causing symptoms that can markedly impair quality of life. Surgical treatment, typically transurethral resection of the prostate (TURP), is highly effective but can be costly and is associated with the risk for significant morbidity. Medical treatments for BPH are targeted toward reducing bladder outlet obstruction either by androgen blockade to reduce prostatic volume or alpha-adrenergic blockade to relax the smooth muscle tone of the prostate. In recent years, understanding of the sympathetic innervation of the prostate has improved. This has been paralleled by the development of alpha-adrenergic blocking agents, from nonselective alpha-antagonists, to selective alpha1-antagonists, to the more selective alpha1A-antagonists. It is anticipated that more specific agents will optimize the therapeutic effectiveness of alpha-adrenergic blockade in the prostate while reducing the side effects associated with alpha-adrenergic blockade in other areas of the body, such as the vascular system. This article reviews the evolution of alpha-blockade therapy in management of BPH, focusing on tamsulosin, an agent targeted toward the alpha1A-adrenoceptor that predominates in the prostate. Clinical trials in Europe and the United States have provided evidence that tamsulosin is effective at doses of 0.4 and 0.8 mg/day. At both doses, tamsulosin is associated with significant improvements in the American Urological Association symptom score and the mean and peak urinary flow rates as compared with placebo. This once-daily alpha1A-adrenergic antagonist is well-tolerated, with a minimal potential for the side effects associated with alphas-blocker therapy.
Publication Types:
Review
Review, tutorial
PMID: 9609620, UI: 98270783

5: Eur Urol 1999;36 Suppl 1:17-22
Adrenoceptor pharmacology: urogenital applications.
Ruffolo RR Jr, Hieble JP
Division of Biological Sciences, SmithKline Beecham Pharmaceuticals, King of Prussia, PA., USA.
Although the selective alpha1-adrenoceptor antagonists were initially developed as antihypertensive drugs, and they are still utilized for this indication, the alpha1-adrenoceptor

blockers are now used extensively for the symptomatic treatment of benign prostatic hyperplasia (BPH). As a result, a number of new drugs in this class have been specifically developed for use in BPH. The utility of alpha1-adrenoceptor antagonists in BPH derives from the observation, made several decades ago, that the irreversible, alpha1- adrenoceptor selectiveantagonist phenoxybenzamine, blocked the contractile activity of norepinephrine in isolated strips of rat or human prostate. Following the further subclassification of alpha1-adrenoceptors into the alpha1A-, alpha1B- and alpha1D-adrenoceptor subtypes, the relationship between subtype selectivity and efficacy in BPH has been investigated in the hope of developing more selective rugs for the treatment of this disorder. Molecular characterization of the adrenoceptor population in human prostate clearly shows the alpha1A-adrenoceptor subtype to predominate, and highly selective alpha1A-adrenoceptor antagonists have been identified and investigated in BPH. However, controversy remains as to whether prostatic smooth muscle contraction is mediated by the alpha1A-adrenoceptor, or by another novel alpha1-adrenoceptor subtype (not corresponding to any of the three known recombinant alpha1-adrenoceptors), or both. (*This indicates there could be a better target, as yet undiscovered. Does SmithKline Beecham have anything in the pipeline?*) Alpha1-Adrenoceptor agonists have been used clinically for the treatment of stress incontinence, acting to increase urethral tone by contracting urethral smooth muscle. Research efforts are ongoing to identify agents of this class having a selective action on urethral versus vascular smooth muscle, in order to produce a greater effect on the urethra without producing dose-limiting increases in blood pressure. Local administration of vascular smooth muscle relaxants, either alone or in combination, has been used for the treatment of erectile dysfunction. An alpha1-adrenoceptor antagonist is often used as onecomponent in such mixtures, which act to relax trabecular smooth muscle. The recent demonstration that a systemically administered drug can produce a sufficiently selective action on cavernosal smooth muscle to allow efficacy without producing limiting systemic side effects has renewed interest in the possibility of systemic administration of alpha1-adrenoceptor antagonists for this indication.
Publication Types:
Review
Review, academic
PMID: 10393468, UI: 99321777

Abbott's Colchicine Site Binding Drug (A-254751)

file: abbott-colchicine

Potential interviewee's for A-254751

Leoni LM, Hamel E, Genini D, Shih H, Carrera CJ, Cottam HB, Carson DA
Department of Medicine and The Sam and Rose Stein Institute for Research on Aging, University of California San Diego, La Jolla 92093, USA. lleoni@ucsd.edu
(*potential interview candidates*)

Verdier-Pinard P, Lai JY, Yoo HD, Yu J, Marquez B, Nagle DG, Nambu M, White JD, Falck JR, Gerwick WH, Day BW, Hamel E
Laboratory of Drug Discovery Research and Development, National Cancer Institute, Frederick Cancer Research and Development Center, Maryland 21702, USA.
(*Good interview candidates.*)

Questions for experts in microtubulin-destabilizing cytotoxic cancer therapies cancer

There are a number of colchincine-site binding agents in preclinical and in clinical trials. Some that we have identified are: combretastatin-A4 (Oxigene), T138607 and T900607(Tularik), Amphethinlle (ICI), 1069C (Wellcome), trimethylcholinic acid (NIH), A-254751 (Abbott), indanocine, tricyclic pyrones, H-10, curacin A,. Are you familiar with some of these? Do any stand out as especially promising?

What is the theorectical reason for targeting the colchicine site?

There are also a number of Vinca-alkaloid site ligands in development, which I believe are also antimitotic agents. Do both types block tubulin formation? Are there any perceived advantages/disadvantages to each target?

The Parke Davis drug, CI-980, was just abandoned in Phase II clinical trials. Since it was in Phase II, was lack of efficay reason for abondonment, or the dose-limiting toxicities seen in Phase I? A number of other colchicine-site drugs have also been abandoned in clinical trials, and I believe none have made it to market? Since all target the colchicine-binding site, could most of the new drugs also suffer the same clinical trial fate. Put another way, what does this say about the prospects for colchicine binding drugs in general?

One drug, the antimitotic H10 is described as a bifunctional anticancer drug: antimitotic and also blocks the cellular transport of to inhibit DNA synthesis. Bifunctionality is perhaps an interesting observation, but is it clinically significant?
A study by Ajinomoto indicated that some tubulin binding agents also exhibit cystostatic antivascular effects. Also, a UCSD study on indanocine states that it is both a cytostatic and

CONFIDENTIAL
JH 003024

cytotoxic agent. Are the antivascular effects due to tubulin binding of fast-growing vasculature at the tumor site, and so are to be expected with all tubulin binding agents?

Questions for Abbott on A-254751 and its competition

The colchicine binding agent, Indanocine, was identified by the National Cancer Institute's Developmental Therapeutics Program as a promising colchicine-site binding agent,which is active in MDR cells. It seems to have the same properties as A-254751? Has anyone licensed from NCI, or is this A254751? How do you view its prospects?

A study by Ajinomoto indicated that some tubulin binding agents also exhibit cystostatic antivascular effects. Also, a UCSD study on Indanocine states that it is both a cytostatic and cytotoxic agent. Does A-254751 exert antivascular effects too? Are the antivascular effects due to tubulin binding of fast-growing vasculature at the tumor site?

The Parke Davis drug, CI-980, was just abandoned in Phase II clinical trials. Since it was in Phase II, was lack of efficacy reason for abandonment, or the dose-limiting toxicities seen in Phase I? A number of other colchicine-site drugs have also been abandoned in clinical trials, and I believe none have made it to market? Since all target the colchicine-binding site, could most of the new drugs also suffer the same clinical-trial fate. Put another way, what does this say about the prospects for colchicine-binding-site drugs in general, in particular? Abbott is already anticipating vasoconstriction risk in humans from its studies in dogs. Why does Abbott think it will not suffer the same fate in human trials?

A study by Ajinomoto indicated that some tubulin binding agents also exhibit cystostatic antivascular effects. Also, a UCSD study on indanocine states that it is both a cytostatic and cytotoxic agent. Does A-254751 exert antivascular effects too? Are the antivascular effects due to tubulin binding of fast-growing vasculature at the tumor site?

Example abstracts

3: Anticancer Drugs 1998 Jun;9(5):405-9
Phase II study of i.v. CI-980 in patients with advanced platinum refractory epithelial ovarian carcinoma.
Kudelka AP, Hasenburg A, Verschraegen CF, Edwards CL, Meyers CA, Varma D, Freedman RS, Forman A, Conrad CA, Grove W, Grothey A, Kavanagh JJ
University of Texas MD Anderson Cancer Center, Houston 77030-4095, USA.

CI-980 is a synthetic mitotic inhibitor that binds to tubulin at the colchicine site, inhibiting the polymerization of microtubules and arresting cellular division in metaphase. Myelosuppression and neurotoxicity were dose-limiting in phase I studies. (*CI-980 is the Parke Davis drug just abandoned in Phase II clinical trials. Since it was in Phase II, was lack of efficay reason for abondonment, or the dose-limiting toxicities seen in Phase I? A number of other colchicine binding drugs have also been abandoned in clinical trials and none have made it to market? Since the mechanism of CI-980 and the other abandoned drugs is the same as the preclinical A-*

CONFIDENTIAL
JH 003025

254751, couldn't A-254751 suffer the same fate. Abbott is already anticipating vasoconstriction risk in humans from its studies in dogs. Why does Abbott think it will not suffer the same fate in human trials?) Sixteen patients with stage III and IV platinum-refractory ovarian cancer received 4.5 mg/m2/day of CI-980 as a continuous i.v. infusion for 72 h, repeated every 3 weeks. Eleven patients had progression and four patients had stable disease. One patient (6%; 95% CI 0-25%) achieved a partial response after 9 months of treatment which lasted for 27 months. The overall median survival was 7 months. Grade 4 granulocytopenia occurred in five patients, with two episodes of neutropenic fever. Neurological toxicity was mild with 12 episodes of transient subclinical recent memory loss documented in four patients by specialized neuropsychological evaluations. One patient each had hallucinations and mild truncal ataxia, and four patients had mild, reversible neurosensory toxicity. One episode of severe hypoxemia and dyspnea occurred in a patient with chronic obstructive pulmonary disease. CI-980 has minimal activity and is tolerable in a population of heavily pretreated patients with platinum refractory ovarian cancer. (*As this is a Phase II trial, the minimal efficacy here may be the reason for abandonment. What does this say about the prospects for colchicine binding drugs in general?*)
Publication Types:
Clinical trial
Clinical trial, phase ii
PMID: 9660537, UI: 98321974

KLOTZ DEPOSITION EXHIBIT 12

D'S EXHIBIT 559

From: Lynn C. Klotz [LynnKlotz@compuserve.com]
Sent: Tuesday, July 18, 2000 6:42 PM
To: Blewitt, Stephen
Subject: First neuropathic pain interview

I got my five minute interview with Mitchell Max of NIH (see attached). I actually got all my key questioned answered. The bottom line is that all drugs for neuropathic pain are mediocre. The questions now are whether the Parke-Davis drug is much, much better than Abbotts, and why have both Merck and Novartis bad-mouthed Abbott?

--Lynn

PENGAD 800-631-6989 EXHIBIT 12 KLOTZ 11-16-06

File: neuropathy

Mitchell Max interview on diabetic neuropathic pain medications

Mitchell B. Max, M.D.
Senior Investigator, Pain and Neurosensory Mechanisms Branch
National Institute of Dental and Craniofacial Research
National Institutes of Health
Building 10, Room 3C-405
Bethesda, MD 20892-1258
tel: 301-496-5483 x405

Dr. Max is the senior author on a recent article entitled "High-dose Oral Dextromethorphan Versus Placebo in Painful Diabetic Neuropathy and Postherpetic Neuralgia." The article reported the results of a human clinical trial.

Interview

The interview summary below was typed from handwritten notes and memory shortly after the interview, and is therefore subject to error in details normal to this process. Some of the interview has been rearranged for clarity. The interviewers comments and questions are in italics, Dr. Max's comments in normal type. This interview summary should remain **confidential** within John Hancock, as I did not ask if it could be disseminated beyond Hancock. Additionally, Dr. Max has had no chance to comment and correct the summaries.

There are a number of adjuvant analgesics in clinical development. Some examples are pregabalin (Parke-Davis) in Phase III trials, GV196771 (Glaxo) in Phase II, mamantine (Merz) in Phase II, ABT-924 (Abbott) which of these--or others that you know of--show special promise for neuropathic pain? Which appear to be unpromising?

The word on the street is that pregabalin appears to be especially promising. It works as well as gabapentin and is safe. I don't know about the Glaxo one. Mamantine looks terrible. ABT-924 nobody really knows yet as Abbott has been rather quiet about it. It looked good in mouse studies, but that may not say much about humans.

I just read two recent abstracts that kind of bad-mouthed ABT-924. They were mouse studies.

Well, then I guess I just don't know.

Some literature studies indicate that some neuropathic pain relievers have small therapeutic windows, which I'll define here as (conc. for intolerable side effects)/(conc. for efficacy). What is an acceptable therapeutic window for pain relievers in general, neuropathic pain relievers? It seems to me that for pain relievers, where a patient might take many more pills than recommended, a therapeutic window of two to three is not sufficient?

For chronic pain medications you just don't have good therapeutic windows. If you get a 25% relief in pain but you are dizzy and can't drive, that might be acceptable. A therapeutic window of two is certainly acceptable.

How do nicotinic acetylcholine receptor agonists stack up against other approaches? For example, in one of your recent papers you studied an N-methyl-D-aspartate (NMDA) receptor atagonist and found it to be promising in low doses.

All approaches are mediocre.

So even a somewhat toxic neuropathic pain medication can get through the FDA as long as it is slightly better than existing ones?

Yes

Thanks for your time, for a very short interview it was certainly informative.

<u>Additional questions for Abbott from what was learned from this interview:</u>

Experts in neuropathic pain point to pregabalin (Parke-Davis, in Phase III trials) as being especially promising. It works as well as gabapentin and is safe. How does ABT-924 stack up against pregabalin? Since pregabalin will likely finish clinical trials before ABT-924, if it is approved is there some chance that it might prevent the approval of ABT-924 if ABT-924 is not significantly better?

KLOTZ DEPOSITION EXHIBIT 13

D'S EXHIBIT 561

From: Lynn C. Klotz [LynnKlotz@compuserve.com]
Sent: Sunday, July 23, 2000 8:44 PM
To: Blewitt, Stephen
Subject: Questions for Abbott

This list of questions can still be culled. Look it over to see if there are a few we can eliminate. If in the end, we e-mail them to Abbott, I would like to proof-read them one more time.

--Lynn

PENGAD 800-631-6989 EXHIBIT DW 13 KLOTZ 11-16-07

CONFIDENTIAL
JH 002984

Questions for Abbott

file: questions-summary

The questions for various basket drugs are organized as follows: All the non cancer drugs, then all the cancer drugs because they have some commonalities. Cytostatic therapy comes before the highly promising endothlin antagonist (ABT-627) which is the last to be discussed simply because the discussion of cytostatic therapies in general lays the ground work for discussion of ABT-627.

ABT-773, ketolide antibiotic for bacteria resistant to antibiotics

To attain a $1 billion market for a ketolide antibiotic as Aventis predicts (and you also predict), one of the experts we interviewed thought that two things must happen. It must unseat erythromycin, and it must out compete the new fluoroquinolones which are going after the same market. Do you agree with that assessment? If so, how do you see the marketing devlop for ABT-773?

Your Phase II clinical data indicates a 92% effectiveness (overall eradication) against *H. Influenzae*. How does this compare to erythromycin? If this indicates that ABT-773 is more effective than erythromycin against *H. Influenzae*, how do you see that affecting market size? Can you break down the increase in market for us.

One expert stated that ketolides have a limited range of bacterial-species activity, which will probably limit their usefulness to respiratory infections. While respiratory infections (sinusitis, bronchitis and pneumonia) are a very large market, do your market estimates include other large markets? If so, why do you think ABT-773 can serve those markets?

Do you see a competitive threat from the new peptide antibiotics such as Daptinomycin?

Ketolides are related to macrolides, for which several resistance mechanisms exist. Do you expect resistance to develop rapidly from some of the minor macrolide resistance mechanisms, even though ketolides have been designed to circumvent the major efflux and ribosomal methylation mechanisms? If not, why?

ABT-594, cholinergic channel modulator for diabetic neuropathic pain

Experts in neuropathic pain point to pregabalin (Parke-Davis, Phase III trials) as being especially promising, because it works as well as gabapentin and is safe. How does ABT-924 stack up against pregabalin? Since pregabalin will likely finish clinical trials and approved (if it is approved) before ABT-924. Although measures have been developed, pain relief is subjective, so demonstrating to the FDA that ABT-594 is more efficacious than gabapentin may be difficult. Could the difficulty of providing convincing statistics might prevent the approval of ABT-924?

One expert stated that all approaches to neuropathic pain are mediocre. Specifically, it has been reported that some of the nicotinic acetylcholine receptor agonists have a small therapeutic window, which we'll define here as:

(conc. for intolerable side effects)/(conc. for efficacy)

From your descriptive memorandum, ABT-594 appears to have a therapeutic window of only two to three. Is this small therapeutic window acceptable? Has the FDA approved neuropathic pain relievers with such a low therapeutic window?

According to one of your own literature publications, a variety of nicotinic acetylcholine receptor agonists such as nicotine, epibatidine and the azetidinyl ether, (R)-5-(2-azetidinylmethoxy-2-chloropyridine (ABT-594) possesses significant efficacy in preclinical models of pain. You do not list any of these others as being in clinical trials. Will any enter trials soon? Do you see any as superior, and only behind in development?

A Merck study claims that in rats "ABT-594 did not cause rotarod impairment at antinociceptive doses but did cause hypothermia and life-threatening adverse effects including seizures." This study also says its results suggest "ABT-594 has nicotine-like dependence liability....These findings indicate that the acute safety profile of ABT-594 is not significantly improved over other nicotinic analgesics." Also, Novartis finds in rats that "ABT-594 dose-dependently increased tail flick latencies but only at doses that also disrupted performance in the rotarod test" Novartis also claims "In all tests, (+)-epibatidine was significantly more potent than ABT-594." According to Abbott, ABT-594 is as efficacious as (+)-epibatidine, which is too toxic for use . How do you explain the differences between your findings in rodents and humans and the Merck and Novartis findings in rodents.

(Note: Animal studies are all studies of nociceptive pain (caused by injurious stimuli, e.g., heat) as opposed to neuropathic pain (caused by never injury). Are there often differences in the effects of anlagesics in the two tests? Are there any animal tests to measure effects on neuropathic pain?)

In an Abbott year 2000 study in rats, ABT-627 (the advanced prostate cancer cytostatic and pain drug) was examined for diabetic neuropathy. How does the promise of ABT-627 compare to ABT-594 for neuropathic pain? Are the two drugs structurally related? Is Abbott heading toward clinical trials with ABT-627 for neuropathic pain?

ABT-980, alpha 1a adrenoceptor antagonist for BPH

In a Chinese literature study comparing a selective (tamsulosin, Flomax) and non-selective (terazosin) alpha 1-adrenoceptor antagonists, tamsulosin showed better results in maximum urinary flow rate (Qmax), and average urinary flow rate (AFR). But the results, in our naive opinion, were not dramatically different. For example AFR increased 37.5% for tamsulosin and 25.8% for Flomax. In your experience, how significant a difference is there in urinary flow rates

between the older drugs terazosin, finasteride, etc., and the new selective drugs like tamsulosin and ABT-980? If there is not much difference, why is tamsulosin use increasing so rapidly? Is it because there is a significant difference of adverse effects with the selective alpha1-adrenoceptor antagonists? What is the adverse effect profile for ABT-980 compared with competitors?

One literature study refers to a patient population that is responsive to alpha1-adrenoceptor antagonists. Does this mean there is a subgroup of patients that don't respond to BPH drugs targeted to alpha1-adrenoceptor? How big is this subgroup?

A-254751, tubulin colchicine-site binding drug to inhibit microtubule formation for advanced cancers

One expert said: of the number of colchicine-site binding agents in preclinical and in clinical trials, combretastatin-A4 (Oxigene, Phase I trails) stands out. He said it is receiving a lot of attention because it is also an antivascular agent. How does A-254751 stack up against combrestatin? How does A-254751 stack up against the many other antimitotic drugs in clinical and preclinical development?

A strikingly large number of colchicine-site drugs have been abandoned in clinical trials. One expert claims the older colchicine-binding drugs failed before they are too toxic. More specifically, the older drugs failed for pharmacokinetic reasons: mainly too long half-lives in the body. He further stated: what one wants are colchicine-binding drugs that get into cells quickly, do their job, and are eliminated from the body quickly. Do you agree with this assessment? What are the pharmacokinetics of A-254751? To what does Abbott attribute its ability to escape MDR?

The same expert says there is one way to increase the probability that a drug will successfully traverse clinical trials–that is to utilize the new sophisticated cell-culture screening capabilities, such as the screening available at the Developmental Therapeutics Program at NCI. For A-254751, has Abbott taken advantage of any of these new cell-culture profiling capabilities? He feels that drugs that do not go through this kind of prescreening may very well fail.

Cytostatic drugs (except for ABT-627, the endothelin ET-1 antagonist)

One literature review indicated that approximately thirty angiostatic agents are undergoing clinical trials, with another fifty agents in preclinical testing. This is a crowded field. While Abbott's approaches are clearly competitive, how can Abbott achieve a large market share given the large number of competitors in this area?

One expert tells us that so far the FDA has not wavered from the strict position of improved survival as the criterion for cancer drug approval. This would include longer survival and improved quality of life. They have not yet approved any drug for slower disease progression. Since cytostatic therapies don't kill tumor cells, the use of time to progression of disease seems

to be the necessary clinical trials measure, What are the problems with this measure? Do you think the difficulty of measuring time to progression, lack of statistically significant evidence of longer survival, and difficulty in determining improved quality-of-life will prolong clinical trails or cause some drugs to fail to get FDA approval? How serious an issue is this?

For any of your cytostatic drugs, have you any data for cost utility = (long-term-cost)/(quality-life-years-saved)? In particular, if there are side-effects, quality-life-years saved may be much less than simply life-years-saved, and cost-utility may be high.

In this regard, metalloproteinase inhibitors are particularly worrisome. One of our experts stated that the metalloproteinase inhibitor BB-94 has "underwhelming" efficacy. It is toxic and causes joint problems. Additionally, one literature study finds that the metalloproteinase inhibitor Marimastat had no survival advantage when compared to chemotherapy with gemcitabine in advanced pancreatic cancer, and Abbott states that Marimastat has dose-limiting joint side-effects. To play devil's advocate, you could argue: Why should the FDA approve a drug that does not prolong a patient's life and at the same time inflicts pain? Could failure for approval of Marimastat make the approval barriers higher for follow-on drugs? What evidence do you have that gelatinase inhibitors like ABT-518 might not have the same FDA approval concerns?

ABT-627, the endothelin ET-1 antagonist

Abbott's internal memorandum describes ABT-627 as a potent vasoconstrictor. Abbott indicated in its internal memorandum that the mechanism of action in prostate cancer wasn't yet known. Additionally, one of our experts said that reducing blood supply to tumor cells was likely not the mechanism by which ABT-627 delays prostate cancer progression, since the cancer metastasizes to bone and is slow growing both indicating there is less need for a good blood supply. What are your latest thoughts about mechanism of action? A competitor who has a better knowledge of mechanism may be in good position to develop a superior drug.

You predict a billion dollar market of A-627, yet its on-the-market competitor Novantrone has only a relatively stagnant market of only $35 million. Could you break down the potential market for A-627 for us? For which patients would it be prescribed? What percentage and yearly number of prostate cancer patients fall into that category?

KLOTZ DEPOSITION EXHIBIT 14

D'S EXHIBIT 804

From: Lynn C. Klotz [LynnKlotz@compuserve.com]
Sent: Tuesday, July 11, 2000 8:55 PM
To: Blewitt, Stephen
Subject: Edit of neuropathic pain summary

I did more searching on the diabetic neuropathic pain situation and found a lot, so I am resending an expanded summary to replace the one I sent earlier. See the attachment.

One interesting abstract I came across indicates that Abbott is trying out its prostate cancer drug on neuopathic pain also (abstract included . This brings up the question whether your royalty rights extend to that indication.

-- Lynn

PENGAD 800-631-6989 EXHIBIT DW 14 KLOTZ 11-16-06

CONFIDENTIAL
JH 003007

Abbott's Neuropathic Pain Agonist (ABT-594)

file: abbott-neuropathic

Potential interviewee's for ABT-594

Belgrade MJ
(*Good interview candidate*)
Fairview Pain Management Center, Fairview-University Medical Center,
Minneapolis, MN 55454, USA. mbelgra1@fairview.org

Morello CM, Leckband SG, Stoner CP, Moorhouse DF, Sahagian GA
(*good interview candidates*)
Veterans Affairs San Diego Healthcare System, Calif 92161, USA.

Questions for experts on neuropathic pain

It is my understanding the tricyclic antidepressants, carbamazepine, gabapentin and amitriptyline are widely used in the treatment of neuropathic pain. Are these drugs sufficient for the need?

There are a number of adjuvant analgesics in clinical development that could compete with nicotinic acetylcholine receptor agonists. Some examples are pregabalin (Parke-Davis) in Phase III trials, GV196771 (Glaxo) in Phase II, mamantine (Merz) in Phase II, which of these--or others that you know of--show special promise for neuropathic pain?

A variety of nicotinic acetylcholine receptor agonists such as nicotine, epibatidine and the azetidinyl ether, (R)-5-(2-azetidinylmethoxy-2-chloropyridine (ABT-594) appear to possesses significant efficacy in preclinical models of pain. Are any of these in clinical trials? Are any especially promising? How do nicotinic acetylcholine receptor agonists stack up against the other kinds of drug candidates (above)?

It has been reported that some of the nicotinic acetylcholine receptor agonists have a small therapeutic window, which I'll define here as:

(conc. for intolerable side effects)/(conc. for efficacy)

What is an acceptable therapeutic window for pain relievers in general, neuropathic pain relievers?
It seems to me that for pain relievers, where a patient might take many more pills than recommended, a therapeutic window of two to three is not sufficient? Comment. What size of therapeutic window does the FDA look for in pain medications?

Questions for Abbott on ABT-594 and its competition

Page 3 in the Abbott report is blank. This is a real page, not just a faxing error, as the next readable page is 4. Was it eliminated for confidentiality reasons?

According to one of your own publications, a variety of nicotinic acetylcholine receptor agonists such as nicotine, epibatidine and the azetidinyl ether, (R)-5-(2-azetidinylmethoxy-2-chloropyridine (ABT-594) possesses significant efficacy in preclinical models of pain. You do not list any of these as being in clinical trials. Will any enter trials? Do you see any as competitors?

It has been reported that some of the nicotinic acetylcholine receptor agonists have a small therapeutic window, which I'll define here as:

(conc. for intolerable side effects)/(conc. for efficacy)

What is an acceptable therapeutic window for pain relievers in general, neuropathic pain releivers? Is there something about diabetic pain that would allow for a small therapeutic window? ABT-594 appears to have a therapeutic window of only two to three (Abbott memorandum p.5). It seems to me that for pain relievers, where patients might take many more pills than recommended, a therapeutic window of two to three is not sufficient? Comment. (Abbott is in Phase IIb clinical trials, which is an indicator of safety but not therapeutic window.) What size of therapeutic window does the FDA look for in pain medications?

A Merck study claims that in rats "ABT-594 did not cause rotarod impairment at antinociceptive doses but did cause hypothermia and life-threatening adverse effects including seizures." This study also says its results suggest "ABT-594 has nicotine-like dependence liability....These findings indicate that the acute safety profile of ABT-594 is not significantly improved over other nicotinic analgesics." Also, Novartis finds in rats that "ABT-594 dose-dependently increased tail flick latencies but only at doses that also disrupted performance in the rotarod test" What does Abbott have to say about these conclusions which indicate (significant?) side-effects at concentrations of use?

It should be noted that animal studies are all studies of nociceptive pain (caused by injuious stimuli, eg. heat) as opposed to neuropathic pain (caused by never injury). Are there often differences in the effects of anlagesics in the two tests? Are there any animal tests to measure effects on neuropathic pain?

Novartis also claims "In all tests, (+)-epibatidine was significantly more potent than ABT-594." According to Abbott, ABT-594 is as efficacious as (+)-epibatidine, which is too toxic for use .)

In an Abbott year 2000 study in rats, ABT-627 (the advanced prostate cancer cytostatic and pain drug) was examined for diabetic neuropathy. How does the promise of ABT-627 compare to ABT-594 for neuropathic pain? Are the two drugs structurally related? Is Abbott heading toward clinical trials with ABT-627 for neuropathic pain?

CONFIDENTIAL
JH 003009

According to one article tricyclic antidepressants and carbamazepine have become the mainstay in the treatment of neuropathic pain. Abbott does not mention carbamazepine for neuropathic pain. How widely is it used? Sales for that indication?

Several studies indicate that gabapentin, although widely used, does not appear to be the most effective for neuropathic pain. For example in one study, "mean pain score and global pain score data indicated no significant difference between gabapentin and amitriptyline. Gabapentin may be an alternative for treating diabetic peripheral neuropathy pain, yet does not appear to offer considerable advantage over amitriptyline and is more expensive." Why has Abbott identified gabapentin as the drug of choice at present?

Example abstracts

1: Pain 2000 Apr;85(3):443-50
Analgesic and toxic effects of ABT-594 resemble epibatidine and nicotine in rats.
Boyce S, Webb JK, Shepheard SL, Russell MG, Hill RG, Rupniak NM
Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, UK. susan_boyce@merck.com
(*Why is Merck publishing on an Abbott drug?*)
The present study directly compared the antinociceptive and toxic effects of the neuronal nicotinic receptor agonist ABT-594(*It is an agonist, not an antagonist*) ((R)-5-(2-azetidinylmethoxy)-2-chloropyridine) with (-)-nicotine and (+)-epibatidine. Like (-)-nicotine (0.8 and 1.6 mg/kg s.c.) and (+)-epibatidine (0.005 and 0.01 mg/kg s.c.), ABT-594 (0.05 and 0.1 mg/kg s.c.) increased response latencies in the hot-plate test in rats, indicating that it has antinociceptive activity. In contrast to (-)-nicotine and (+)-epibatidine, ABT-594 did not cause rotarod impairment at antinociceptive doses but did cause hypothermia and life-threatening adverse effects including seizures. (*Merck claims ABT-594 causes life-threatening seizures in rats. What is Abbott'r response*?) ABT-594 (0.01 and 0.1 mg/kg i.v.) also produced a dose-dependent increase in blood pressure resembling that observed with (-)-nicotine (0.03, 0.1 and 0. 03 mg/kg i.v.) and (+)-epibatidine (0.001 and 0.003 mg/kg i.v.). Both the antinociceptive and toxic effects (convulsions and hypertension) were abolished by pretreatment with the brain penetrant neuronal nAChR antagonist mecamylamine (1 mg/kg s.c.; i.v. for cardiovascular studies), demonstrating that these actions of ABT-594 were mediated via activation of neuronal nicotinic receptors. Continuous infusion of ABT-594 (0.2 mg/kg per day s.c.) to rats for 7 days followed by challenge with mecamylamine (1 mg/kg i.p.) induced a nicotine-like abstinence syndrome suggesting that ABT-594 has nicotine-like dependence liability. These findings indicate that the acute safety profile of ABT-594 is not significantly improved over other nicotinic analgesics. (*"other nicotinic analgesics" indicates that ABT-594 is not alone. Are others on the market?*) (*What does Merck have to say about these conclusions? It should be noted that this is a study of nociceptive pain (caused by injuious stimuli, elg. heat) as opposed to neuropathic pain(caused by never injury).*)
PMID: 10781917, UI: 20245628

CONFIDENTIAL
JH 003010

4: Biochem Pharmacol 1999 Sep 15;58(6):917-23
Therapeutic potential of neuronal nicotinic acetylcholine receptor agonists as novel analgesics.
(Abbott calls these novel analgesics; in contrast to the Merck article which states "acute safety profile of ABT-594 is not significantly improved over other nicotinic analgesics.")
Decker MW, Meyer MD
Neurological and Urological Diseases Research, Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL 60064-6125, USA. michael.decker@abbott.com
Pharmacological treatments for pain have come largely from two classes of compounds--the opioids and the nonsteroidal anti-inflammatory drugs (NSAIDs). Because of deficiencies associated with these two classes of compounds, exploration of novel approaches to pain relief has intensified of late. Nicotine, a neuronal nicotinic acetylcholine receptor (nAChR) agonist, has long been known to have antinociceptive effects in both experimental animals and humans. The relatively modest antinociceptive effects and the toxicities associated with nicotine preclude its development as an analgesic agent. However, recent discoveries in the nAChR field have stimulated interest in nAChR-targeted compounds as potential analgesic agents. Epibatidine, a potent nAChR agonist, was found to have full efficacy relative to opioids in preclinical pain models. Although epibatidine is toxic, these observations demonstrated that modest efficacy is not a general limitation of nAChR agonists. Moreover, exploration of the molecular biology of nAChRs revealed evidence of receptor diversity, suggesting that nAChR subtype-selective agents less toxic than nicotine might be discovered; and early medicinal chemistry efforts already have resulted in compounds with improved safety profiles. For example, ABT-594 is a nAChR agonist with the antinociceptive efficacy of epibatidine, but with an improved safety profile.*(With a therapeutic window of only 2,[Abbott memorandum p.----) , is the saftey profile improved enough for FDA approval? Abbott is in Phase IIb, which is an indicator of safety. For pain relievers, which might be abused by people in pain, is a therapeutic window of 2 enough?)* This commentary reviews recent findings with nAChR-targeted compounds, explores potential mechanisms responsible for nAChR-mediated antinociception, and raises issues that must be addressed in developing compounds of this class as analgesics.
Publication Types:
Review
Review, tutorial
PMID: 10509744, UI: 99437443

1: Clin J Pain 2000 Jun;16(2 Suppl):S49-55
The treatment of neuropathic pain: antidepressants and opioids.
Watson CP
Department of Medicine, University of Toronto, Ontario, Canada.
(Interview candidate)
[Medline record in process]
OBJECTIVE: The objective of this article was to review the positive scientific data on antidepressants and opioids, which are largely confined to randomized controlled trials in two neuropathic pain conditions that have proved to be good models for clinical investigation. These two disorders are postherpetic neuralgia and painful diabetic neuropathy. DESIGN: This is a review of the literature using MEDLINE, CINAHL, and the Cochrane Database. RESULTS: There is extensive literature supporting the use of the older antidepressants such as amitriptyline

in neuropathic pain. Newer randomized controlled trials support the use of opioids. CONCLUSIONS: First-line therapy for neuropathic pain may be either an older generation antidepressant such as amitriptyline or nortriptyline or the anticonvulsant gabapentin. For refractory cases, chronic opioid therapy may be the only avenue of relief, and evidence is accumulating that this approach is safe if proper guidelines are observed.
PMID: 10870740, UI: 20326555

5: Eur J Pharmacol 2000 Jan 24;388(1):29-35
ABT-627, an endothelin ET(A) receptor-selective antagonist, attenuates tactile allodynia in a diabetic rat model of neuropathic pain.
(Is Abbott's prostate cancer cytostatic and pain drug the same as the one for diabetic neuropathy, but just under a different name?)
Jarvis MF, Wessale JL, Zhu CZ, Lynch JJ, Dayton BD, Calzadilla SV, Padley RJ, Opgenorth TJ, Kowaluk EA
Neurological and Urological Diseases Research and Metabolic Diseases Research, Pharmaceutical Products Division, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6123, USA. michael.jarvis@abbott.com
Tactile allodynia, the enhanced perception of pain in response to normally non-painful stimulation, represents a common complication of diabetic neuropathy. The activation of endothelin ET(A) receptors has been implicated in diabetes-induced reductions in peripheral neurovascularization and concomitant endoneurial hypoxia. Endothelin receptor activation has also been shown to alter the peripheral and central processing of nociceptive information. The present study was conducted to evaluate the antinociceptive effects of the novel endothelin ET(A) receptor-selective antagonist, 2R-(4-methoxyphenyl)-4S-(1,3-benzodioxol-5-yl)-1-(N, N-di(n-butyl)aminocarbonyl-methyl)-pyrrolidine-3R-carboxylic acid (ABT-627), in the streptozotocin-induced diabetic rat model of neuropathic pain. Rats were injected with 75 mg/kg streptozotocin (i. p.), and drug effects were assessed 8-12 weeks following streptozotocin treatment to allow for stabilization of blood glucose levels (>/=240 mg/dl) and tactile allodynia thresholds (</=8.0 g). Systemic (i.p.) administration of ABT-627 (1 and 10 mg/kg) was found to produce a dose-dependent increase in tactile allodynia thresholds. A significant antinociceptive effect (40-50% increase in tactile allodynia thresholds, $P<0.05$) was observed at the dose of 10 mg/kg, i.p., within 0.5-2-h post-dosing. The antinociceptive effects of ABT-627 (10 mg kg(-1) day(-1), p.o.) were maintained following chronic administration of the antagonist in drinking water for 7 days. In comparison, morphine administered acutely at a dose of 8 mg/kg, i.p., produced a significant 90% increase in streptozotocin-induced tactile allodynia thresholds. The endothelin ET(B) receptor-selective antagonist, 2R-(4-propoxyphenyl)-4S-(1, 3-benzodioxol-5-yl)-1-(N-(2, 6-diethylphenyl)aminocarbonyl-methyl)-pyrrolidine-3R-carboxy lic acid (A-192621; 20 mg/kg, i.p.), did not significantly alter tactile allodynia thresholds in streptozotocin-treated rats. Although combined i.p. administration of ABT-627 and A-192621 produced a significant, acute increase in tactile allodynia thresholds, this effect was significantly less than that produced by ABT-627 alone. These results indicate that the selective blockade of endothelin ET(A) receptors results in an attenuation of tactile allodynia in the streptozotocin-treated rat. *(This year 2000 study is in rat. How does the promise of ABT-627 (Abbott's prostate drug compare to ABT-594 for neuropathic pain? Is Abbott heading toward clinical trials with ABT-627 for neuropathic pain?)*

PMID: 10657544, UI: 20125915

Anticonvulsant drugs for acute and chronic pain.
Wiffen P, McQuay H, Carroll D, Jadad A, Moore A
Cochrane Pain, Palliative and Supportive Care CRG, Pain Research Unit, Churchill Hospital, Old Road, Headington, OXFORD, UK, OX3 7LJ. phil.wiffen@pru.ox.ac.uk
BACKGROUND: Anticonvulsant drugs have been used in the management of pain since the 1960s. The clinical impression is that they are useful for neuropathic pain, especially when the pain is lancinating or burning. OBJECTIVES: To evaluate the analgesic effectiveness of anticonvulsant drugs compared to either placebo or other drugs in order to provide evidence-based recommendations for pain management in clinical practice and to identify a clinical research agenda. Adverse effects are also considered. SEARCH STRATEGY: Randomised trials of anticonvulsants in acute, chronic or cancer pain were identified by Medline (Silver Platter 3.0, 3.1 and 3.11) from 1966 to February 1994. In addition, 40 medical journals were hand searched (published between 1950 and 1990). Additional reports were identified from the reference list of the retrieved papers, and contacting investigators. Date of the most recent searches: 1994. SELECTION CRITERIA: Randomised trials reporting the analgesic effects of anticonvulsant drugs in patients, with pain assessment as either the primary or a secondary outcome. DATA COLLECTION AND ANALYSIS: Data were extracted by two independent reviewers, and trials were quality scored. Numbers-needed-to-treat (NNTs) were calculated from dichotomous data for effectiveness, adverse effects and drug-related study withdrawal, for individual studies and for pooled data. MAIN RESULTS: Twenty trials of four anticonvulsants were considered eligible (746 patients). The only placebo-controlled study in acute pain found no analgesic effect of sodium valproate. Three placebo-controlled studies of carbamazepine in trigeminal neuralgia had a combined NNT for effectiveness of 2.6, for adverse effects 3.4, and for severe effects (withdrawal from study) 24. Three placebo-controlled studies of diabetic neuropathy had a combined NNT for effectiveness of 3, for adverse effects 2.5, and for severe effects 20. Three placebo-controlled studies of migraine prophylaxis had a combined NNT for effectiveness of 2.4, for adverse effects 2.4 and for severe effects 39. Phenytoin had no effect in irritable bowel syndrome, and carbamazepine little effect in post-stroke pain. Clonazepam was effective in one study of temporomandibular joint dysfunction. No study compared one anticonvulsant with another. Anticonvulsants fared poorly against other treatments. REVIEWER'S CONCLUSIONS: Although anticonvulsants are used widely in chronic pain surprisingly few trials show analgesic effectiveness. No trial compared different anticonvulsants. There is no evidence that nticonvulsants are effective for acute pain. In chronic pain syndromes other than trigeminal neuralgia anticonvulsants should be withheld until other interventions have been tried. (*This confirms Abbott's contention that there is a significant unmet need here.*)
Publication Types:
Review
Review, academic
PMID: 10796752, UI: 20257832

KLOTZ DEPOSITION EXHIBIT 15

D'S EXHIBIT 805

From: Lynn C. Klotz [LynnKlotz@compuserve.com]

Sent: Friday, July 28, 2000 10:55 AM

To: Blewitt, Stephen

Subject: Abbott interview writeup

See attached. Overall, most questions were answered satisfactorally--certainly no indication of any deception on Abbott"s part. Only one question needs following up, the patent question on ABT-594. Let's talk to see where we go from here, and to discuss the format of the final report.

-- Lynn

File: interview-abbott

Telephone Interview with Abbott, Conducted by L. Klotz (consultant) and S. Blewitt.

Representing Abbott:

John Leonard, Vice President of Development
Phil _______, Corporate Licensing
Steve Cohen, Controller

[Steve, do you have full names and formal titles for the Abbott participants?]

Almost all answers were provided by John Leonard, as the other two Abbott participants were not scientists and this was a technically oriented interview. Interviewer questions and comments are in italics, Abbotts response in normal type.

ABT-773, ketolide antibiotic for bacteria resistant to antibiotics

To attain a $1 billion market for a ketolide antibiotic as Aventis predicts (and you also predict), one of the experts we interviewed thought that two things must happen. It must unseat erythromycin, and it must out compete the new fluoroquinolones which are going after the same market. Do you agree with that assessment? If so, how do you see the marketing devlop for ABT-773?

Erythromycin was unseated a decade ago, the erythromycin derivative zitromax has $600 to $700 US sales and over $1 billion worldwide. It has 15% market share [*of the deriviative market?*].
[He mentioned a few other big sellers, from which it might be concluded that there is a very big total market in which Abbott could achieve a significant market share.]

Fluoroquinolones in the past were used for urinary tract infections, but their marketers are trying to move into the respiratory infection market.

Ketolides are related to macrolides, for which several resistance mechanisms exist. Do you expect resistance to develop rapidly from some of the minor macrolide resistance mechanisms, even though ketolides have been designed to circumvent the major efflux and ribosomal methylation mechanisms?

In the US, efflux is the major mechanism of resistance. I believe in Japan the ribosomal mechanism may be important too. ABT-773 was originally designed and synthesized to avoid efflux. It has demonstrated efficacy on normally antibiotic resistant cells. We are about to enter Phase III trials.

One expert stated that ketolides have a limited range of bacterial-species activity, which will

probably limit their usefulness to respiratory infections. While respiratory infections (sinusitis, bronchitis and pneumonia) are a very large market, do your market estimates include other large markets? If so, why do you think ABT-773 can serve those other markets?

ABT-773 was designed first and foremost for respiratory indications.

Your Phase II clinical data indicates a 92% effectiveness (overall eradication) against H. Influenzae. How does this compare to erythromycin? If this indicates that ABT-773 is more effective than erythromycin against H. Influenzae, how do you see that affecting market size? Can you break down the increase in market for us.

Very early on we specifically designed our clinical trials to look at *H. Influenzae*, "which sets the bar" for these antibiotics. ABT-773 is as good or maybe better, but the study was small.

Do you see a competitive threat from the new peptide antibiotics such as Daptinomycin?

They are low on our radar screen, because they are IV administered. ABT-773 is for ambulatory patients, who have a cough, a stuffy nose. The IV administered antibiotics are for hospital use. We are developing an IV form of ABT-774, to compete in that market, but the market is small, and we haven't really talked too much about this.

ABT-594, cholinergic channel modulator for diabetic neuropathic pain

Experts in neuropathic pain point to pregabalin (Parke-Davis, Phase III trials) as being especially promising, because it works as well as gabapentin and is safe. How does ABT-924 stack up against pregabalin? Pregabalin will likely finish clinical trials and be approved (if it is approved) before ABT-924. Although measures have been developed, pain relief is subjective, so demonstrating to the FDA that ABT-594 is more efficacious than gabapentin may be difficult. Could the difficulty of providing convincing statistics prevent the approval of ABT-924?

We haven't compared the two drugs head-to-head, but from what we see in the pregablin literature, we believe our drug is good. I doubt that the FDA would use pregablin as a standard for approval. In the neuropathic pain area, there are no standards. The last drug was approved 40(?) years ago. We see no approval risk for ABT-594 from pregablin. Also ABT-594 works through a different mechanism. There is a great need for drugs in the neuropathic pain area.

From your descriptive memorandum, ABT-594 appears to have a therapeutic window of only two to three. Is this small therapeutic window acceptable? Has the FDA approved neuropathic pain relievers with such a low therapeutic window?

Aspirin has a therapeutic window of only ten. For ABT-594, maybe we will be able to get a theoretical window greater than five. When we give patients the upper-limit dose, the side effects aren't dangerous: headache, vomiting. These minor side effects appear to go away over time.

A Merck study claims that in rats "ABT-594 did not cause rotarod impairment at antinociceptive doses but did cause hypothermia and life-threatening adverse effects including seizures." This study also says its results suggest "ABT-594 has nicotine-like dependence liability....These findings indicate that the acute safety profile of ABT-594 is not significantly improved over other nicotinic analgesics." Also, Novartis finds in rats that "ABT-594 dose-dependently increased tail flick latencies but only at doses that also disrupted performance in the rotarod test" Novartis also claims "In all tests, (+)-epibatidine was significantly more potent than ABT-594." According to Abbott, ABT-594 is as efficacious as (+)-epibatidine, which is too toxic for use. How do you explain the differences between your findings in rodents and humans and the Merck and Novartis findings in rodents?

Someone called my attention to the Merck study, I don't think I've seen the Novartis one. However, in clinical studies I would trade five million rats for a hundred people.

Why are Merck and Novartis taking "pot shots" at you?

I think Merck and Novartis are using us as a standard. We are the only drug to compare with. Merck bought Sybia, the company which has rights to many of the receptors like the one we are targeting.

Is ABT-594 clear of the Sybia's patents?

ABT-594 was prior to the Sybia/Merck arrangement. Future products must avoid Sybia's rights.

[*Note: this did not actually answer whether Abbott has an invention prior to Sybia, or if Sybia's patents may cover the receptor for Abbott's drug. We should clarify this.*]

In an Abbott year 2000 study in rats, ABT-627 (the advanced prostate cancer cytostatic and pain drug) was examined for diabetic neuropathy. How does the promise of ABT-627 compare to ABT-594 for neuropathic pain? Are the two drugs structurally related? Is Abbott heading toward clinical trials with ABT-627 for neuropathic pain?

Yes, we have looked at ABT-627 as an analgesic, it has limited value for pain, so we won't pursue it.

ABT-627 also might be used to treat cardiovascular disease. We don't serve that market, so we won't pursue that indication for business reasons.

<u>ABT-980, alpha 1a adrenoceptor antagonist for BPH</u>

In a Chinese literature study comparing selective (tamsulosin, Flomax) and non-selective (terazosin) alpha 1-adrenoceptor antagonists, tamsulosin showed better results in maximum urinary flow rate (Qmax), and average urinary flow rate (AFR). But the results, in our naive opinion, were not dramatically different. For example, AFR increased 37.5% for tamsulosin and

25.8% for Flomax. I know these drugs sell well, but I am not sure why.
In our human trials we look at flow, and we look at symptoms. Treating the symptoms is important. For example does the bladder empty completely, is urgency to urinate reduced or eliminated.

We have completed Phase II, clinical trials and are about to enter Phase III. Our data so far, show that ABT-980 is virtually super imposable on Flomax, maybe we are slightly better in a few areas.

At what point does the FDA say, OK we have a number of products on the market which are not improvements over the previous ones, we won't approve the next one because patients don't need another similar product?

This is an incremental product, a lot of what our industry does is incremental products. So it becomes a marketing and pricing issue. The FDA doesn't make decisions based on the number of products already on the market. In Europe, where prices are controlled, if a product is a me-too product, it can enter the market but at a lower price.

One literature study refers to a patient population that is responsive to alpha1-adrenoceptor antagonists. Does this mean there is a subgroup of patients that don't respond to BPH drugs targeted to alpha1-adrenoceptor? How big is this subgroup?

I can't answer that; on one has carried out pharmacogenetic studies. The subgroup referred to could be those whose prostate is so big, nothing short of surgery will help them.

A-254751, tubulin colchicine-site binding drug to inhibit microtubule formation for advanced cancers

One expert said, of the number of colchicine-site binding agents in preclinical and in clinical trials, combretastatin-A4 (Oxigene, Phase I trails) stands out. He said it is receiving a lot of attention because it is also an antivascular agent. How does A-254751 stack up against combrestatin?

I don't know.

A strikingly large number of colchicine-site drugs have been abandoned in clinical trials. One expert claims the older colchicine-binding drugs failed before they are too toxic. More specifically, the older drugs failed for pharmacokinetic reasons: mainly too long half-lives in the body. He further stated: what one wants are colchicine-binding drugs that get into cells quickly, do their job, and are eliminated from the body quickly. Do you agree with this assessment? What are the pharmacokinetics of A-254751? How does the drug escape MDR?

I can't give you the pharmacokinetic data from memory.

Could we look at it?
Yes, I can get it for you.

[*Since A-254751 is in early stage clinical trials, the data may give us some insight about its prospects. But I am already rating this drug as only having a fair chance of FDA approval based on the fate of the other colchicine-site binding agents. I don't see that the data can change that opinion, so I withdrew the request to see it.*]

We don't know how the drug escapes the MDR mechanism.

How does A-254751 compare to other colchicine-site binding agents regarding toxicity?

We think the window is pretty good compared to others.

<u>*Cytostatic drugs (except for ABT-627, the endothelin ET-1 antagonist)*</u>

One literature review indicated that approximately thirty angiostatic agents are undergoing clinical trials, with another fifty agents in preclinical testing. This is a crowded field. While Abbott's approaches are clearly competitive, how can Abbott achieve a large market share given the large number of competitors in the cytostatic area in general?

I agree that for cytostatic drugs in general their may be 50 to 200 in testing. To get the market lead, get one that works. In this business, there are a number of people who start things, many more than the ones who finish.

One expert tells us that so far the FDA has not wavered from the strict position of improved survival as the criterion for cancer drug approval. This would include longer survival and improved quality of life. They have not yet approved any drug for slower disease progression. Since cytostatic therapies don't kill tumor cells, the use of time to progression of disease seems to be the necessary clinical trials measure. What are the problems with this measure? Do you think the difficulty of measuring time to progression, lack of statistically significant evidence of longer survival, and difficulty in determining improved quality-of-life will prolong clinical trails or cause some drugs to fail to get FDA approval? How serious an issue is this?

You set this question up too starkly. Clearly drugs that make people to live longer, as long as they maintain a quality of life, are likely to be approved. With ABT-627, we are working with the FDA to determine what is a meaningful clinical progression. We are working with the FDA every step of the way.

For any of your cytostatic drugs, have you any data for cost utility = (long-term-cost)/(quality-life-years-saved)? In particular, if there are side-effects, quality-life-years saved may be much less than simply life-years-saved, and cost-utility may be high.

We haven't done cost-utility precisely, but we compare favorably with other products–for

example, ABT-627 compares favorably with Luprolide, a chemical castration drug with sales of $800 million. Also, Luprolide is very expensive.

In this regard, metalloproteinase inhibitors are particularly worrisome. One of our experts stated that the metalloproteinase inhibitor BB-94 has "underwhelming" efficacy. It is toxic and causes joint problems. Additionally, one literature study finds that the metalloproteinase inhibitor Marimastat had no survival advantage when compared to chemotherapy with gemcitabine in advanced pancreatic cancer, and Abbott states that Marimastat has dose-limiting joint side-effects. To play devil's advocate, you could argue: Why should the FDA approve a drug that does not prolong a patient's life and at the same time inflicts pain? Could failure for approval of Marimastat make the approval barriers higher for follow-on drugs? What evidence do you have that gelatinase inhibitors like ABT-518 might not have the same FDA approval concerns?

British Biotech was first with Marimastat, so it has the problems of being first. One thing Abbott has learned from Marimastat is that it is not selective enough. Abbott's metalloproteinase inhibitor avoids blocking a particular enzyme that is needed to keep joints clear. Abbott's drug does not create what we call "frozen shoulder." There is a good animal model that we use for frozen shoulder.

<u>ABT-627, the endothelin ET-1 antagonist</u>

Abbott's internal memorandum describes ABT-627 as a potent vasoconstrictor. Abbott indicated in its internal memorandum that the mechanism of action in prostate cancer wasn't yet known. Additionally, one of our experts said that reducing blood supply to tumor cells was likely not the mechanism by which ABT-627 delays prostate cancer progression, since the cancer metastasize to bone and is slow growing both indicating there is less need for a good blood supply. What are your latest thoughts about mechanism of action? A competitor who has a better knowledge of mechanism may be in good position to develop a superior drug.

Yes, we agree that the mechanism of action for metastacized prostate cancer is not vasoconstriction. We do have knowledge about mechanism for prostate cancer.

[*The interview ended here because Steve Cohen had an important meeting to attend. There was little need for additional questions on ABT-627 as well.*]

KLOTZ DEPOSITION EXHIBIT 17

D’S EXHIBIT 806

JOHN HANCOCK LIFE INSURANCE COMPANY
Bond & Corporate Finance Group

Report Date:	September 21, 2000
Recommendation to B.I.C.:	September 21, 2000
Report to C.O.F.:	October 10, 2000

Private

Purchase Recommendation

GBSA	$110 mm	GBRE	$20 mm
CLDBLK	$ 30 mm	OPNBLK	$ 4 mm
PENPAR	$ 9 mm	IQA	$15 mm
LOLA	$ 8 mm	GRPLTC	$ 4 mm
RETLTC	$ 7 mm	GRPINS	$ 2 mm
BOLI	$ 4 mm	UNIVRSL	$ 5 mm
IPLI	$ 2 mm		

ABBOTT LABORATORIES ("Non-Recourse")
North Chicago, IL

We are recommending a $220 million commitment to fund research and development expenses for a basket of eight pharmaceutical products ("Program Compounds") currently under development by Abbott Laboratories ("Abbott"). The commitment will be funded over a four-year period and will be subject to Abbott Laboratories co-funding at least two times our commitment on the Program Compounds during the same period of time. In return for the research and development payments, Abbott will agree to pay John Hancock milestone and royalty payments for each Compound that reaches regulatory approval and has commercial sales. The purpose of this transaction is to allow Abbott to increase its expenditures on research and development (to generate future growth in revenues and earnings) but to maintain current earnings.

The Program Compounds are a diversified pool of eight compounds owned by Abbott Laboratories and in various stages of clinical development. The Compounds are divided between late-stage and early-stage, including three Phase III, two Phase II, one Phase I, and two pre-clinical compounds. The Compounds are well-diversified from a disease/stage perspective, although several compounds are focused on the cancer market. Even within the cancer market, though, each of the Compounds targets either different types of cancer, or different mechanisms of action. Based on their current stage of development and projected sales levels, we think that the Program Compounds have a current market value of approximately $1 billion. During the term of the transaction, we expect Abbott to spend approximately $1.3 billion (including John Hancock's commitment) on further research and development for the Compounds.

Through the management fee and anticipated milestone payments, we expect to generate at least an 8% return on investment during the initial four years of the transaction. The average return is approximately 17.5% over 15 years. If we assume that we could sell our future royalty stream after the fifth year, our average five-year IRR would be about 22%.

The transaction is structured to provide a one-to two percent probability of total loss combined with a one-to-two percent chance of not earning a return. This is approximately equivalent to a 60 basis point annual loss over five years – or a "Ba1" credit rating. The expected return of 17.50% is attractive relative to the risk of the transaction.

Report Authors:
Stephen J. Blewitt, Managing Director
Scott Hartz, Managing Director
(t:\industrials\sjb\yellows\abbott-yo3.doc)

CONFIDENTIAL
JH 001203

EXHIBIT
17
Klotz 11-16-07
PENGAD 800-631-6989

JOHN HANCOCK LIFE INSURANCE COMPANY
Bond & Corporate Finance Group

Report Date:	September 21, 2000
Recommendation to B.I.C.:	September 21, 2000
Report to C.O.F.:	October 10, 2000

Private

Purchase Recommendation

GBSA	$110 mm	GBRE	$20 mm
CLDBLK	$ 30 mm	OPNBLK	$ 4 mm
PENPAR	$ 9 mm	IQA	$15 mm
LOLA	$ 8 mm	GRPLTC	$ 4 mm
RETLTC	$ 7 mm	GRPINS	$ 2 mm
BOLI	$ 4 mm	UNIVRSL	$ 5 mm
IPLI	$ 2 mm		

ISSUER: **Abbott Laboratories** (Non-recourse)

ISSUE: $220 million Research and Development Funding Commitment

ISSUE RATING: JH: Ba2

BROKER: Direct

SIC CODE: 2830 – Drugs

USE OF PROCEEDS: To fund the research and development of eight pharmaceutical products ("Program Compounds") owned Abbott, and to pre-fund management fees and projected milestone payments, and to pay for transaction and administrative expenses.

STATE OF INC.: Illinois

CIRCLE DATE: August 31, 2000

TAKEDOWN DATE: Upon completion of documentation

PROGRAM PAYMENTS: During the Program Term, and in consideration of Abbott's continuing performance of the research services under the Research Plan, John Hancock shall make program payments to Abbott in the installments and on the dates set forth below:

Date	Payment
[December,] 2000	$50,000,000
[December,] 2001	$55,000,000
[December,] 2002	$55,000,000
[December,] 2003	$60,000,000

"Program Term" means the period commencing [December,] 2000 Date and ending on [December,] 2004.

"Research Plan" means a detailed statement of Abbott's objectives, activities, timetable, FTE allocation and budget for the Program Compounds during the Program Compounds during each year of the Program Term. Abbott shall provide an updated research plan on an annual basis.

Abbott Obligations

During the Program Term, Abbott agrees to spend, in addition to the funds provided by John Hancock, (i) a minimum of $50 million per year and (ii) a minimum of $400 million in aggregate on research and development programs associated with the Program Compounds.

Program Payment Termination Provisions

Unless the parties agree upon an alternative arrangement, if Abbott (a) ceases research and development of all Program Compounds or (b) does not spend at least the amount provided by John Hancock in a year on the research and development of Program Compounds or (c) does not reasonably demonstrate, in its updated research plan, its intent to spend a minimum of the amount provided by John Hancock in the next year of the Program Term or $620 million (including the funds provided by John Hancock) in aggregate, John Hancock's obligation to continue to make Program Payments shall cease. In the case of either (a) or (b) above, Abbott will refund to John Hancock $55 million minus half of the amount actually spent by Abbott during that year.

Carryover Provisions

If Abbott spends the amount provided by John Hancock in a year but does not spend at least an additional $50 million, Abbott agrees to spend the difference between $105 million and the amount actually spent in that year (the "Carryover Amount") in the subsequent year. John Hancock's obligation to make Program Payments in the subsequent year, if any, will be deferred until that time that Abbott demonstrates that it has spent the Carryover Amount in that subsequent year.

If Abbott spends the amount provided by John Hancock in each year and at least an additional $50 million in each year, but does not spend a minimum of $620 million (including the funds provided by John Hancock) in aggregate on research and development programs associated with the Program Compounds during the Program Term, Abbott agrees to spend the difference between $620 million and the aggregate amount actually spent (the "Aggregate Carryover Amount") in the subsequent year. If Abbott does not spend the Aggregate Carryover Amount in the subsequent year, Abbott will refund to John Hancock one-third of the difference between (a) $620 million and the amount actually spent.

MANAGEMENT FEE: Commencing with the first anniversary of the Program Term and continuing until the end of the Program Term, Abbott shall pay John Hancock a fee in the amount of $2.0 million per year as compensation for monitoring Abbott's continuing performance of its research services under the Research Plan, the development of the Program Compounds, and to reimburse John Hancock for its ongoing fees and expenses incurred in connection with this transaction.

CONFIDENTIAL
JH 001205

MILESTONE PAYMENTS:	Abbott shall make the following payments for each compound for each milestone achieved after commencement of the Program Term:

Upon the allowance of an IND application by the FDA:	$1,000,000
Upon the initiation of a Phase I Clinical Trial:	$2,000,000
Upon the initiation of a Phase II Clinical Trial:	$3,000,000
Upon the initiation of a Phase III Clinical Trial:	$4,000,000
Upon the filing of an NDA application with the FDA:	$5,000,000
Upon NDA Approval by the FDA:	$10,000,000

Aggregate milestone payments paid by Abbott, for all "non-NDA Approval" milestones achieved will not exceed $12 million. Aggregate milestone payments paid by Abbott, for all "NDA Approval" milestones achieved will not exceed $40 million. In addition, "non-NDA Approval" milestone payments will not exceed $3 million in the first year or $6 million in the second year after commencement of the Program Term.

ROYALTY PAYMENTS: Abbott shall pay to John Hancock royalties on aggregate worldwide Net Sales of Program Compounds (all Program Compound sales combined) at the following rates:

Annualized Net Sales of Aggregate Program Compounds	Royalty Rate
$0 to $400 million	8%
>$400 million and ≤ $1,000 million	4%
>$1,000 million and ≤ $2,000 million	1%
>$2,000 million	½%

The obligation to make royalty payments shall commence on the date of the First Commercial Sale of a Program Compound and shall continue with respect to Net Sales of such Program Compound for a period of ten years. Not withstanding the foregoing, the obligation to make royalty payments on all Program Compounds shall not begin until after the second anniversary of the Program Term and shall cease at December 31, 2014.

HANCOCK HOLDINGS:	None
RELATED HOLDINGS:	$29,000,000 Preferred Stock of Metabolex Corporation with Put Rights to Abbott
ANALYST:	Stephen J. Blewitt
HOUSE COUNSEL:	Amy Weed
SPECIAL COUNSEL:	Choate, Hall & Stewart

Report Authors:
Stephen J. Blewitt, Managing Director
Scott Hartz, Managing Director
(t:\industrials\sjb\yellows\abbott-yo3.doc)

CONFIDENTIAL
JH 001206

TRANSACTION OVERVIEW

In December 1999, John Hancock approached Abbott Laboratories, Inc. ("Abbott") with a financial structure that would allow Abbott to increase its research and development expenditures (to generate future growth in revenues and earnings) but maintain current earnings. The structure, which is presented in this investment recommendation, uses probability analysis on a diversified portfolio of drug compounds, supplemented by scientific due diligence, to achieve an investment grade or near investment grade risk for John Hancock and allow us to generate equity returns in the form of current (royalty) income for a sizeable investment.

This transaction requires John Hancock to commit to funding an average of $55 million per year for a period of four years to fund the research and development of a diversified pool of eight compounds ("Program Compounds") owned by Abbott Laboratories. We have valued the Program Compounds today at approximately $1 billion (or five times our investment) and we expect Abbott to spend over seven times our investment during the term of the transaction (during the initial four year period, Abbott will commit two times John Hancock's investment for those compounds). In return for the research and development payments, Abbott will agree to pay John Hancock milestone and royalty payments for each compound that reaches regulatory approval and has commercial sales as well as a management fee.

Through the management fee and anticipated milestone payments, we expect to generate at least an 8% return on investment during the initial four years of the transaction. The average return is approximately 17.5% over 15 years. If we assume that we could sell our future royalty stream after the fifth year, our average five-year IRR would be about 22%.

This transaction is consistent with our approach to investing in the pharmaceutical sector. During the past five years, we have invested approximately $460 million in pharmaceutical companies. Approximately $300 million is invested in straight debt for investment grade companies. The remaining $160 million is invested in equity-oriented transactions where we think that there are opportunities for exceptional value. Although we have invested in a couple of straight equity transactions, approximately $150 million of the $160 million is invested in transactions where our downside risk is protected by either "put rights" to investment grade companies (Metabolex, Nexell), senior note positions (Celgene, Cubist), or structured portfolios of drug candidates (Pharma Marketing). In these transactions, we maintain sizable up-side potential but reduce the probability of losing all of our invested capital through the structure of our investment.

In summary, we think that the structure of this transaction, which has us co-investing with Abbott Laboratories in a diversified pool of their drug compounds, which we believe have a current value of approximately $1 billion, over a four year period, during which time Abbott has to meet co-investment obligations and the drug compounds need to continue to progress in development, allows us to generate substantial current income that exceeds the risk associated with the transaction. Although we are committing to a substantial $220 million investment, our expectation is that our net investment will not exceed $176 million (due to management fees, milestone payments, and royalty payments).

The transaction is structured to provide a one-to-two percent probability of total loss combined with a one-to-two percent chance of not earning a return. This is approximately equivalent to a 60 basis point annual loss over five years – or a "Ba1" credit rating. The expected return of 17.50% is attractive relative to the risk of the transaction.

CONFIDENTIAL
JH 001207

Expected accounting treatment

There have been a number of royalty streams sold off in the form of an asset backed security. The most visible example is the David Bowie bond bought by Prudential Insurance. While this royalty transaction has many similar features, it is also different in that it is funded over a four year period and no royalties are currently being generated. We believe that at the end of the funding period we will be able to obtain a rating on the transaction that will allow it to be placed on our bond schedule. In the meantime, it will appear on our BA schedule. We plan to account for this investment using the guidance in ruling 9920 of the Emerging Issues Task Force. Ruling 9920 requires that each year, or more often if the assumptions change, we will project the expected cash flows and book income equal to the internal rate of return. Any changes to the expected cash flows will be spread over the remaining life of the transaction through the newly calculated IRR. This is the same method we use to account for our CBO equity investments. Initially we expect the IRR on this investment to be approximately 17%.

OVERVIEW OF ABBOTT LABORATORIES

Abbott Laboratories is engaged in the discovery, development, manufacture and sale of healthcare products and services. Abbott has five reporting revenue segments: Pharmaceutical Products, Diagnostic Products, Hospital Products, Ross Products and International. It also has a 50%-owned joint venture, TAP Holdings, Inc. The principal products of the Pharmaceutical Products Division are the anti-infectives clarithromycin, agents for the treatment of epilepsy, migraine and bipolar disorder, including Depakote; urology products, including Flomax for the treatment of BPH; Abbokinase, a thrombolytic drug, and the anti-viral Norvir, a protease inhibitor for the treatment of HIV. The Diagnostic Division's products include diagnostic systems and tests for blood banks, hospitals, and commercial laboratories. The Hospital Products Division sells drugs and drug delivery systems, intensive care products, cardiovascular products, renal products, and intravenous and irrigation solutions. The Ross Products Division sells adult and pediatric nutritionals such as Similac, Isomil, Ensure, Glucerna, and Pedialyte. The International Division's products include a broad line of hospital, pharmaceutical, and adult and pediatric nutritional products marketed and primarily manufactured outside the United States.

For the year ended December 31, 1999, Abbott had revenues and net income of approximately $13.2 billion and $2.4 billion, respectively. Abbott is rated "Aaa" by the major rating agencies. As of September 18, 2000, Abbott had a market capitalization of approximately $74 billion.

ABBOTT LABORATORIES
CONSOLIDATED STATEMENT OF OPERATIONS

($ in thousands)	Fiscal Years Ended December 31,		
	1997	1998	1999
Net Sales	$11,889	$12,512	$13,177
Costs and expenses:			
Cost of goods sold	5,052	5,406	5,977
Selling, general and administrative	2,695	2,759	2,857
Research and development	1,307	1,228	1,193
Total operating expenses	9,055	9,395	10,028
Operating income	2,833	3,117	3,149
Net interest expense	85	102	81
Other charges	(186)	(223)	(330)
Income (loss) before taxation	2,934	3,241	3,396
Net income (loss)	$2,079	$2,331	$2,445

CONFIDENTIAL
JH 001208

TRANSACTION DETAILS

A. PROGRAM COMPOUNDS

There are eight Program Compounds included in this transaction. The Compounds are divided between late-stage and early-stage, including three Phase III, two Phase II, one Phase I, and two pre-clinical compounds. The Compounds are well-diversified from a disease/stage perspective, although several compounds are focused on the cancer market. Even within the cancer market, each of the Compounds targets either different types of cancer, or different mechanisms of action. The products are described more fully below:

Product	Indication	JH Est. Peak Sales ($mm)	Stage of Development
ABT 980 (BPH)	Treatment of benign prostatic hyperplasia	600	Development Stage: Phase III Expected Launch: 2003
ABT 773 (Ketolide)	Antibiotic	800	Development Stage: Phase III Expected Launch: 2003
ABT 627 (Endothelin)	Treatment of prostate cancer	700	Development Stage: Phase III Expected Launch: 2003
ABT 594 (CCM)	Non-opiod, non-NSAID analgesic	700	Development Stage: Phase II Expected Launch: 2004
E7010 (Anti-mitotic)	Cancer	500	Development Stage: Phase I/II Expected Launch: 2004
MMPI	Cancer	400	Development Stage: Phase I Expected Launch: 2005
FTI	Cancer	400	Development Stage: Pre-clinical Expected Launch: 2005
Urokinase	Cancer	400	Development Stage: Pre-clinical Expected Launch: 2005

B. SUMMARY OF ESTIMATED SALES

In estimating sales projections by Program Compound, we started with determining the expected peak sales for each Compound. We have conservatively estimated the peak sales for each Compound based on our evaluation of market potential for each Compound relative to results for other similar drugs and expected competitive drugs. In general, our level of peak sales is significantly below Abbott's level (approximately 25%) -- but, because of the tiered royalty structure, the relative economic difference is not significant. Our next step was to use a Sales Curve calculated by Lehman Brothers that projects ramp-up and ramp-down for sizeable drugs. In general, this Curve shows peak sales being reached seven years after launch. Ramp-up is achieved by 5% of peak sales in the first year, followed by 13%, 25%, 50%, 80%, and 90%. Peak sales are maintained for three years, and the compound then achieves 85% of peak, 75%, 70%, etc. As expected, every compound has its own unique curve, and Lehman's is only a general estimate. We have compared the curve to IMS data of prescription sales for individual compounds in a number of drug classes from 1981 to 1999. Our analysis indicates that Lehman's curve is a good fit and we have applied that curve. The table below shows projected sales for each Compound and probability-weighted estimated sales for the entire portfolio of Compounds.

ESTIMATED SALES PROJECTION

($ in millions) Name	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Projected Sales												
ABT-980 (BPH)	30	78	180	300	480	540	600	600	600	510	0	0
ABT-627 (Endothelin)	35	91	210	350	560	630	700	700	700	595	0	0
ABT-773 (Ketolide)	40	104	240	400	640	720	800	800	800	680	0	0
ABT-594		35	91	210	350	560	630	700	700	700	595	0
E7010 (Anti-mitotic)		20	52	120	200	320	360	400	400	400	340	0
MMPI												
FTI			20	52	120	200	320	360	400	400	400	340
Urokinase												
Total Projected Sales	105	328	793	1,432	2,350	2,970	3,410	3,560	3,600	3,285	1,335	340
Estimated Sales	76	225	531	932	1,510	1,837	2,068	2,129	2,138	1,908	530	74

For projection purposes, MMPI, FTI and Urokinase are considered as one Program Compound with a Phase I probability of success.

C. MILESTONE AND ROYALTY PAYMENTS

Under the Agreement, Abbott agrees to pay to John Hancock royalties on aggregate worldwide Net Sales of Program Compounds (all Program Compound sales combined) at the following rates: 8% on the first $400 million, 4% on the next $600 million, 1% on the next $1 billion, and ½% on any amount above $2 billion. Abbott's obligation to make royalty payments will commence on the date of the First Commercial Sale of a Program Compound and will continue with respect to Net Sales of such Program Compound for a period of ten years. Not withstanding the foregoing, the obligation to make royalty payments on all Program Compounds will not begin until after the second anniversary of the Program Term and will cease at December 31, 2014. Based on our estimate of aggregate sales for the Program Compounds, we expect the following amounts of Royalty Payments:

($ in millions) Name	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Estimated Sales	76	225	531	932	1,510	1,837	2,068	2,129	2,138	1,908	530	74
Royalty Payments												
8.0% on $400 mm	6	18	32	32	32	32	32	32	32	32	32	6
4.0% on $400-$1,000	0	0	5	21	24	24	24	24	24	24	5	0
1.0% on $1,000 - $2,0	0	0	0	0	5	8	10	10	10	9	0	0
0.5% on $2,000+	0	0	0	0	0	0	0	1	1	0	0	0
Total Royalty Pymts	6	18	37	53	61	64	66	67	67	65	37	6
(average percent)	8.0%	7.0%	5.7%	4.0%	3.5%	3.2%	3.1%	3.1%	3.1%	3.4%	7.0%	8.0%

CONFIDENTIAL
JH 001210

In addition to the Royalty Payments, Abbott will be obligated to make payments to John Hancock for certain milestones achieved for each compound. The milestone and the corresponding payments are described below. Aggregate milestone payments paid by Abbott, for all "non-NDA Approval" milestones achieved will not exceed $12 million. Aggregate milestone payments paid by Abbott, for all "NDA Approval" milestones achieved will not exceed $40 million. In addition, "non-NDA Approval" milestone payments will not exceed $3 million in the first year or $6 million in the second year after commencement of the Program Term.

Upon the allowance of an IND application by the FDA:	$ 1,000,000
Upon the initiation of a Phase I Clinical Trial:	$ 2,000,000
Upon the initiation of a Phase II Clinical Trial:	$ 3,000,000
Upon the initiation of a Phase III Clinical Trial:	$ 4,000,000
Upon the filing of an NDA application with the FDA:	$ 5,000,000
Upon NDA Approval by the FDA:	$10,000,000

Based on the number of Compounds in the Program and the number of potential milestones for each Compound, we expect to receive $3 million, $6 million, and $3 million of "non-NDA" milestone payments in the first three years. In addition, we expect to receive $20 million in 2003 and $10 million in 2004 for NDA Approvals.

In aggregate, the management fees, milestone payments, and royalty payments are approximately 4.3% of Net Sales of the Program Compounds. The tiered structure of the royalty payments and the up-front milestone payments, however, substantially reduce the downside of the transaction in the event that aggregate net sales are below our expected case. For example, if sales were 25% below projected, a flat 4.3% royalty rate would yield a loss ratio of 4% versus a loss ratio of 1.6% when using the tiered structure.

D. ESTIMATED CASH FLOW PROJECTIONS

Based on the calculations of Net Sales and Milestone and Royalty Payments, which are described above, the Cash Flow of this transaction is as presented in the table below. In particular, the structure provides for adequate current income during the first two-to-three years when there are no approved Compounds, and substantial current royalty income based on Net Sales of approved Compounds.

($ in millions) Name	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
JH Cash Payments	(50)	(55)	(55)	(60)											
Management Fee	0	2	2	2	2										
Milestone Payments	0	3	6	23	10										
Royalty Payments	0	0	0	6	18	37	53	61	64	66	67	67	65	37	6
Aggregate Cash Rcv'd	0	5	8	31	30	37	53	61	64	66	67	67	65	37	6
JH Net Cash Flow	(50)	(50)	(47)	(29)	30	37	53	61	64	66	67	67	65	37	6

The projected bond equivalent yield for this transaction is approximately 17.5% and the cash to invested capital ratio is 2.7 times.

CONFIDENTIAL
JH 001211

E. SUMMARY BUDGET

Abbott will be using the funds from this transaction to invest in the research and development of a specific pool of drug compounds, and to pre-fund management fees and projected milestone payments. These funds will be part of a total investment by Abbott of approximately $1,300 million during the next ten years and $900 million over the four year co-investment period. In addition, based on the stage of the development of the Program Compounds, and their expected sales, we have valued the Program Compounds today at approximately $1 billion. Our valuation is based on our knowledge of "out-licensing" transactions between pharmaceutical companies and the milestone and royalty structure that is market for different stage compounds. In general, out-license transactions provide the licensor with a royalty rate of between 10% (for Phase I compounds) to 30% (for Phase III compounds) and a 50/50 split for compounds that have completed Phase III. Using an average 20% royalty applied to estimated sales and a 15% discount rate, we arrived at a value of approximately $1 billion.

The following table summarizes the Company's expected budget during the Program Period:

($ in millions)

Name	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
Projected Budget												
ABT-980 (BPH)	80	40	30	30	20	20	10	10	10	10	10	270
ABT-627 (Endothelin)	40	40	20	20	20	20	20	10	10	10	10	220
ABT-773 (Ketolide)	135	60	42	42	27	27	27	17	17	17	17	428
ABT-594	70	80	30	20	20	20	20	20	10	10	10	310
E7010 (Anti-mitotic)	20	30	35	20	30	10	10	5	5	5	5	175
MMPI	20	30	35	20	23	15	15	5	5	5	5	178
FTI	5	10	37	17	15	15	5	5	5	5	5	124
Urokinase	15	25	35	33	15	15	5	5	5	5	5	163
Total Projected Budget	385	315	264	202	170	142	112	77	67	67	67	1,868
Estimated Budget	327	250	201	134	90	81	66	45	40	40	40	1,314

CONFIDENTIAL
JH 001212

TRANSACTION ANALYSIS

The structure of this transaction (which includes a diversified pool of eight Abbott compounds, and a tiered royalty structure) offers a substantial likelihood that we will receive a long-term bond equivalent yield of approximately 17.5% which is substantially greater than the inherent risk of the transaction.

Expected Return.

Methodology

Determining the fair economics of the proposed transaction is highly dependent upon the number of compounds included, the characteristics of the compounds (i.e. status of development, potential sales), the structure of the royalty rates, and an estimation of what is a fair return. To help us answer these questions, we have taken several steps. First, we have researched industry standards for likelihood of success and probable sales curves for compounds in different stages of development. Second, we have developed a spreadsheet model that calculates the rate of return for a chosen portfolio and have developed a minimum number of compounds and associated milestone/royalty payments to provide us with returns that adequately compensate us for the risk we are taking. Third, we have tried to determine what rate of return the capital markets would require for the level of risk that we are willing to take.

The Program Compounds consist of five of Abbott's late-stage development compounds and a basket of three pre-clinical cancer compounds. The late-stage compounds range from mid-Phase II to starting Phase-III. Peak annual sales for these compounds range from $400 million to $800 million. With the exception of the "cancer basket", the compounds are independent of each other. Our due diligence provided us with results consistent with Abbott's representations and expectations for the Program Compounds, although we have scaled back sales projections significantly.

> Our scientific and market diligence for the portfolio of compounds consisted on a number of steps. As a first step, we received internal scientific and business write-ups from Abbott for each Program Compound. The material provided by Abbott demonstrated the scientific rationale for the compounds, results of clinical trials, and a competitive analysis. Through financial reports, we searched for all references to Abbott's compounds and all references to competitive compounds in the same class or same disease category. We used this information to evaluate the potential size of markets for the Program Compounds and their competitive landscape. We engaged Dr. Lynn Klotz to search the major drug and medical databases for scientific reports on the Program Compounds and competitive compounds in the same class or same disease category. We used this information to evaluate, from a scientific perspective, what research scientists had discovered about the Program Compounds from an efficacy and safety perspective. We also used this information to identify potential experts to contact for additional questions. Finally, Dr. Klotz contacted the experts on a non-disclosure basis (not revealing that we were looking at Abbott compounds) and asked the experts to assess the Program Compounds and any potential competitive products from an efficacy and market potential perspective. In summary, none of our diligence revealed any information that was materially different than what Abbott had provided to us.
>
> Dr. Lynn Klotz is a former professor of Biochemistry and Molecular Biology at Harvard University and a former officer of two biotechnology companies, BioTechnica and Codon. Dr. Klotz is currently an independent consultant. His most recent assignment was as a member of a four-person team consulting with the President of Mississippi State University to provide a strategic plan for their Life Sciences Institute.

Probabilities of Success
Based on the development stage of each compound, we assigned probabilities of success ("regulatory approval") and time to success for each compound. Our probabilities of success come from a 1995 study by Dr. Joseph A. DiMasi at the Tufts Center for the Study of Drug Development, and were modified based on our specific knowledge of the Program Compounds. Dr. DiMasi's study is generally accepted by the pharmaceutical industry as an accurate assessment of the probability of success and of the time and costs associated with drug development. Dr. DiMasi looked at a random sample of 93 compounds in four broad disease categories from 12 pharmaceutical companies that were first tested in humans between 1970 and 1982.

Dr. DiMasi's results are summarized below:

PROBABILITY OF SUCCESS

Entering Phase	NSAID	Cardio-vascular	Anti-infective	Neuro-pharm	All
I	22%	26%	30%	20%	23%
II	30%	41%	38%	22%	31%
III	71%	72%	77%	51%	63%

Dr. DiMasi calculated the average time to approval as 8.75 years for compounds entering Phase I, 7.5 years for compounds entering Phase II, and 5.5 years for compounds entering Phase III. Embedded in these times was an approximately 30-month review process by the FDA. Due to legislative and process changes, the average FDA review time is now approximately 12 months. A revised timeframe for approval (which was been published by TCSDD in 1999), based on accelerated review by the FDA, and quicker processes within the pharmaceutical companies, is 6.0 years for Phase I, 5.0 years for Phase II, and 3.0 years for Phase III.

Sales Estimates
In estimating sales projections by Program Compound, we started with determining the expected peak sales for each Compound. We have conservatively estimated the peak sales for each Compound based on our evaluation of market potential for each Compound relative to results for other similar drugs and expected competitive drugs. In general, our level of peak sales is significantly below Abbott's level (approximately 25%) -- but, because of the tiered royalty structure, the relative economic difference is not significant. Our next step was to use a Sales Curve calculated by Lehman Brothers that projects ramp-up and ramp-down for sizeable drugs. In general, this Curve shows peak sales being reached seven years after launch. Ramp-up is achieved by 5% of peak sales in the first year, followed by 13%, 25%, 50%, 80%, and 90%. Peak sales are maintained for three years, and the compound then achieves 85% of peak, 75%, 70%, etc. As expected, every compound has its own unique curve, and Lehman's is only a general estimate. We have compared the curve to IMS data of prescription sales for individual compounds in a number of drug classes from 1981 to 1999. Our analysis indicates that Lehman's curve is a good fit and we have applied that curve. The table below shows projected sales for each Compound and probability-weighted estimated sales for the entire portfolio of Compounds.

Financial Model and Results
We've modeled the returns on this portfolio of drugs using a Monte Carlo simulation and assuming their probabilities of success are independent. Let's start, however, with some simplifying assumptions to get better intuition on the risk of the transaction. Assume the probability of success of each drug is 50%, the drugs are independent, and that the success of any one drug will give us a return of 8% on the transaction. In this case, we will lose all our investment only if all the drugs fail. The probability of this is $(1/2)^6 = 1.6\%$. Spread over a 4 year duration, the expected annual loss is 40 basis points which implies the same risk as a Baa3 bond. If only one drug is successful, which should occur with the probability of $(1/2)^6 * (6!/1!) = 6/64 = 9.4\%$, the return, in our simplified model, is 8% on the entire investment. This is approximately 200 basis points over Treasuries. If two or more drugs are successful, the structure caps the investment's return at

approximately 20%. The probability of this is 100% –1.6% - 9.4% = 89%. Hence, the weighted average return on the investment is 1.6%*0 + 9.4%*8% + 89%*20% = 18.5%.

This example is obviously a simplification. Each of the drugs has a different probability of success, depending upon how far along each is in the approval process, and a different revenue profile. To reflect the different probabilities and different revenue streams, we developed a spreadsheet model that incorporates multiple drug compounds (and their specific probability of success, time to launch, and expected sales pattern) and a variable milestone/royalty structure. We then ran the spreadsheet model 500 times to provide us a range of outcomes as well as the expected results for returns and losses.

In our base case, we have made the following assumptions·

Product	Phase	JH Probability Of Approval	Launch	JH Peak Sales
BPH	Phase III	65%	2003	$600 mm
Ketolide	Phase III	70%	2003	$800 mm
Endothelin	Phase III	70%	2003	$700 mm
CCM	Phase II	50%	2004	$700 mm
Antimitotic	Phase I/II	40%	2004	$500 mm
MMPI	Phase I	10%	2005	$400 mm
FTI	PC	10%	2005	$400 mm
Urokinase	PC	10%	2005	$400 mm

... and calculated the average bond equivalent yield of this scenario to be approximately 17.3%. It is important to note that the expected IRRs are over a long period of time (15 years). Assuming that we could sell our future royalty stream after the fifth year, our five-year IRR would be about 22%.

Analysis of Return

The last step of our analysis was to determine what a fair economic return for this transaction should be. We have benchmarked this transactions in a number of ways, such as: R&D vehicles for pre-clinical compounds were sold with expected IRRs (over a three-to-five year period) of approximately 40%; Hambrecht & Quist has estimated pharmaceutical IRRs for single phase-II compounds to be 40% and single phase-III compounds to be 25%; the Palisade Partners (Sony movies) transaction that we participated in last year has an expected IRR of 20%; Elan Pharmaceuticals' pooled transaction has an expected five-year IRR of 13%; limited partner equity funds have about a 25% expected net IRR; and our proprietary analysis of the equity market's IRR for Abbott's entire R&D pipeline of 16-22%. Based on these comparisons, we think that an IRR of 17% over a long period of time is reasonable.

We also evaluated the relationship between our investment (and Abbott's) in the entire portfolio and the average royalty rate that we expect to receive – which is approximately 4-5%. We estimate that the current value of the compounds that Abbott is contributing to the transaction is about $1 billion. During the four year investment period, Abbott expects to invest $800 million on the compounds, in addition to our $200 million. Based on these amounts, our investment is approximately 10% of the total invested dollars. Most pharmaceutical companies earn about a 50% pre-tax margin (excluding R&D expenses) on sales. On a net basis, then, our expected royalty and milestone percentage should be about 5%.

CONFIDENTIAL
JH 001215

Risk Analysis.

The fundamental risks of this transaction are whether Abbott receives marketing approval from the FDA for a sufficient number of the Program Compounds and whether the commercial success of the Compounds are as we expect. In developing the *expected return*, we have made a number of reasonable assumptions regarding the probability of obtaining FDA approvals, acceptance of the products in the marketplace and competition. In many cases, our assumptions are significantly more conservative than Abbott's.

Again looking at our base case (which is demonstrated in the Chart I on the next page), the probability of no successful drugs is approximately 1.7% (the bar on the left). There are also a number of scenarios that produce a return of approximately 1% – 2%. These scenarios arise when only a cancer drug is successful. The cancer drugs have lower anticipated revenues, as well as lower probabilities of success, than any of the other drugs. This represents about 1.6% of the scenarios. All other scenarios give us a return of 9% or more. Assuming a 1-2% return represents a loss of half our original investment, the expected loss in this simulation is 1.7% + ½*1.6% = 2.5%. Spread over a four year duration, the annual expected loss is 62 basis points which corresponds to the risk of a Ba1 rated bond.

We also ran a downside simulation, where the probabilities of success are discounted by 25% from the DiMasi study and the expected revenues are discounted by 25% from our base case (this is shown in Chart II on the next page).

The average return in this downside scenario is 9.3%. The probability that no drugs are successful rises dramatically to 4.9%. The low return scenario is now even lower (-2%) and also has a higher probability (2.7%). So, the annual expected loss is (4.9% + .6*2.7%)/4 = 165 basis points which corresponds to the risk of a B1 rated bond.

CONFIDENTIAL
JH 001216

CHART I

BASE CASE

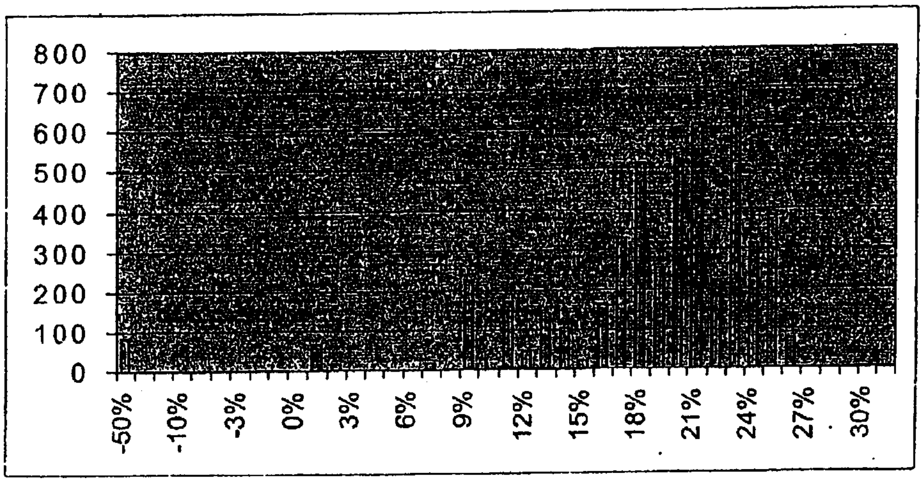
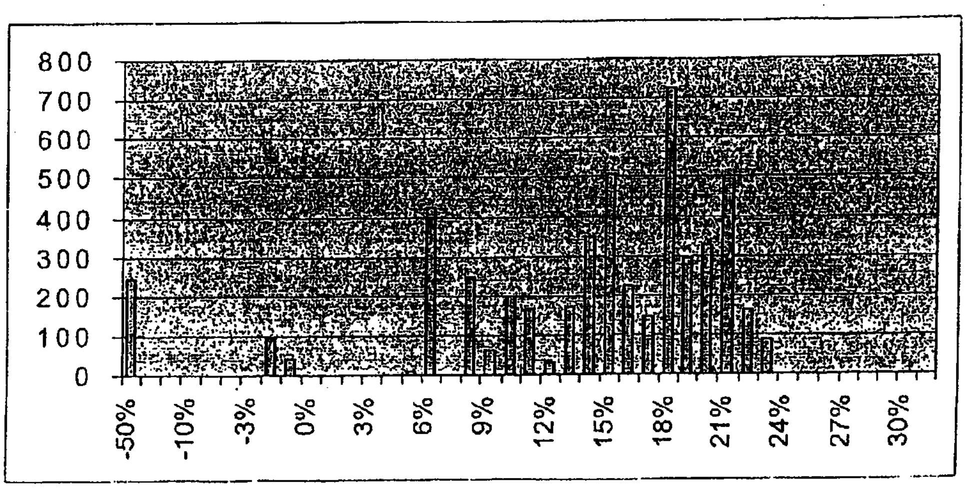


CHART II

DOWNSIDE SCENARIO



CONFIDENTIAL
JH 001217

APPENDIX
PRODUCT DESCRIPTIONS

ABT-980

ABT-980 is a selective alpha blocker for the treatment of benign prostatic hyperplasia ("BPH"), a disorder that effects approximately 10 million middle-aged and elderly males in the U.S. The primary sympton of BPH is obstruction of urinary outflow and increased frequency of urination. Global sales of BPH products is approximately $2 billion and is expected to continue to grow as the population ages and as better treatments become available. Currently, alpha blockers, including Abbott's Hytrin which recently became generic, are the most frequently prescribed pharmaceutical treatment for BPH. ABT-980 has the benefit of other alpha blockers, but since it only inhibits alpha receptors in the urinary tract, side effects on the cardio-vascular system and central nervous system are expected to be reduced substantially.

One other selective alpha blocker, Boehringer Ingelheim's Flomax, the FDA and has been on the market since 1999. Flomax's current sales are approximately $300 million. Abbott completed Phase II clinical trials and entered Phase III trials this past summer. In its Phase II trials, Abbott demonstrated that it is effectively equivalent (based on safety and efficacy) to Flomax.

This month, Abbott has learned that in long-term studies with rats, that about 15% of the rats given ABT-980 developed gallstones. Abbott does not know if these results are applicable to humans and at what frequency; however, there is no evidence of gallstones in humans to-date. In addition to its usual clinical trials, Abbott will try to determine whether gallstones will develop in humans over the long-term and what implications that may have. If ABT-980 fails due to this gallstone issue, Abbott will replace ABT-980 with another compound.

Abbott expects to submit ABT-980 for approval in June 2002 and launch the product in August 2003. The patent on ABT-980 expires in 2016.

E-7010

E-7010 is a compound that Abbott licensed from Eisai Co. Ltd. in July 2000. E7010 has completed Phase I trials for various oncology applications. E7010 is an oral medication with a unique mechanism of action that enables it to stop cell mitosis with fewer side effects than current cytotoxic therapies. Although financial terms of the Abbott-Eisai agreement have not been publicly disclosed. Abbott is committing $25 million in up-front and milestone payments to Eisai and will pay a double-digit royalty percentage on net sales. As a result of in-licensing E7010, Abbott has discontinued development of its own internally developed "anti-mitotic" compound.

Anti-mitotic compounds are not new. Taxol, the largest selling cancer drug, is an anti-mitotic. E7010, however, binds to a different site of a cell's microtubules than Taxol, and inhibits cell proliferation in a unique manner which is believed to cause fewer side effects.

E7010 has successfully completed Phase I clinical trials in Japan. These trials may be repeated in the U.S. but Abbott expects to move quickly into Phase II trials. Abbott expects to submit E7010 for approval in 2003 and launch the product in 2004. The patent on E7010 expires in 2011.

Our scientific consultants, Dr. Dennis A. Carson, UCSD School of Medicine, and Dr. John Kavanaugh, Jr., MD Anderson Cancer Center, did not have specific knowledge about the Abbott/Esai compound. However, each researcher provided us with consistent critical benchmarks to evaluate the compound (such as whether the compound has been tested against specific cancer cell lines, whether the compound has been tested in combination with other anti-cancer agents. We have confirmed that Abbott independently addressed these critical benchmark and received positive results.

ABT-773 (Ketolide)

ABT-773 is a member of a novel group of ketolide antibiotics within the macrolide group of antimicrobials. Ketolides have a similar mechanism of action to other macrolides such as Pfizer's *Zithromax* and Abbott's

Biaxin. Unlike macrolide antibiotics, ketolides are active against *s. pneumonia* and *h. influenza*. The antibiotics market size is approximately $25 billion; macrolides account for approximately 13% and have an increasing market share. Only one ketolide (*Ketek*) is in advanced clinical trials; this compound, discovered by Aventis, was approved for sale in Europe and was been submitted to the FDA for approval in February 2000. Aventis expects to launch *Ketek* in 2001.

ABT-773 entered Phase III clinical trials this past summer. Abbott expects to submit ABT-773 for approval in June 2002 and launch the product in August 2003. The patent on ABT-773 expires in 2016.

Our scientific consultant, Dr. Robert C. Moellering, Jr., Harvard Medical School and Beth Israel Medical Center, confirmed the scientific rationale for ketolides and their market potential. Based on information that he has seen, Dr. Moellering believes that ABT-773 has more promise than Aventis' *Ketek*.

ABT-594

ABT-594 is a non-opiod, non-NSAID analgesic compound that is orally-administered for the treatment of diabetic neuropathic pain. In animal models, the compound has been shown to be substantially more potent than morphine with a better side effect profile. Neuropathic pain is a substantial and underserved market. Approximately 4-5 million people are thought to suffer from neuropathic pain but only a few medications provide complete pain relief and most medications have significant side effects. As more effective and tolerable medications become available, the neuropathic pain market is expected to experience significant growth.

ABT-594 is currently in Phase II clinical trials. If Phase II and Phase III trials are successful, Abbott expects to submit ABT-594 for approval in May 2003 and launch the product in July 2004. The patent on ABT-594 expires in 2016.

Our scientific consultant, Dr. Mitchell Max, NIH, eliminated an initial concern of ours that the "therapeutic window" of ABT-594 was too short and would potentially block approval. Dr. Max indicated that ABT-594's therapeutic window was acceptable. Dr. Max was not able to fully address toxicity issues raised by two of Abbott's competitors that the compound demonstrated opiod-like side effects in mice. These toxicity issues have not been found by Abbott in its mice or human trials. Dr. Max believed that ABT-594 showed a good profile in mice.

ABT-627

ABT-627 is an inhibitor of a family of endothelin peptides that cause constriction of vascular muscles and stimulate cell proliferation. ABT-627 is currently being developed by Abbott for the treatment of prostate cancer, and other cancer types.

Prostate cancer ("PCA") is the most common cancer to strike non-smoking men. Approximately 1.7 million men live with prostate cancer in the U.S., and there are approximately 180,000 newly diagnosed cases each year. The primary treatment of advanced stage PCA is hormone therapy. Patients receiving hormone therapy become resistant to this treatment after two to three years and then have a life expectancy of only about twelve months.

The primary benefit of ABT-627 is to reduce the pain associated with PCA and to delay the progression of the disease (but not necessarily improve survival).

ABT-627 is currently in Phase III clinical trials. If Phase III trials are successful, Abbott expects to submit ABT-627 for approval in December 2003 and launch the product in June 2004. The patent on ABT-627 expires in 2015.

Our scientific consultant, Dr. Joel Byron Nelson, MD, University of Pittsburgh, has indicated that ABT-627 is safe, significantly reduces pain associated with PCA, and delays disease progression.

MMPI

MMPI is an inhibitor of enzymes called matrix metalloproteinase that degrade a wide range of protein substrates. High expression of these enzymes occurs in cancer and is associated with the ability of tumors to grow, invade, develop new blood vessels and metastasize.

The MMPI field is competitive. More than 30 firms have filed patents and several companies have compounds in advanced clinical development. Abbott's MMPI has the potential competitive advantage of a better side effect profile. It appears to exhibit less arthritis and tendonitis of the upper joints that its competitors. This compound is currently being evaluated in Phase I clinical trials.

Abbott hopes to submit MMPI for approval in 2004 and launch the product in 2005. The patent on MMPI expires in 2018.

FTI

FTI is an inhibitor of enzymes called farnesyltransferase that assist certain proteins, such as the Ras protein, which are critical for malignant growths.

The FTI field is competitive. Approximately four compounds are in clinical development, and an additional five are in pre-clinical studies. Abbott has not yet chosen a specific FTI to enter into human clinical trials. It expects to enter human clinical trials in 2001

Abbott hopes to submit FTI for approval in 2004 and launch the product in 2005. The patent on FTI is not expected to expire prior to 2014.

Urokinase

Urokinase is an inhibitor of enzymes called urokinase which are believed to promote the metastases of tumors by breaking down cell membranese.

The Urokinase field is less well-developed than MMPI and FTI. No compound has currently made it into clinical trials. Abbott is currently evaluating several compounds. If Abbott fails to take a Urokinase compound into clinical trials, Abbott will substitute another Phase I compound into the Program.

Abbott hopes to submit Urokinase for approval in 2004 and launch the product in 2005. The patent on Urokinase is not expected to expire prior to 2014.

Our scientific consultant, Dr. Edward Sausville, National Cancer Institute, has indicated that "cytostatic" therapies such as MMPI, FTI and Urokinase may be useful upon recurrence of cancer as a means to stopping the progression of the disease. He believes that they will be useful in combination with other therapies and may not be exceptional compounds by themselves.

CONFIDENTIAL
JH 001220

KLOTZ DEPOSITION EXHIBIT 18

D'S EXHIBIT 502

Steve,

This packet contains:

- An invoice for my time on this project.

- A draft report entitled "Expected Internal Rate of Return," which is both a lay-level explanation of the approach to evaluating investments in drugs in development and the mathematical derivations. The report is nearly in publication form, but without Figure 1. Figure 2 is included separately; that is, not attached to the report.

  You probably only want to read the first two sections, unless you feel your college-level mathematics is up to it. I can explain the rest to you when we get together. Perhaps an half-hour talk to you, someone who is mathematically and Excel knowledgeable in your group, and whoever is working on the pharmaceutical side with you.

- The spread sheet and example results comparing my three-linear sales curve with the OTA sales curve. The example results are summarized in the report.

- Another spread sheet and example results using the three-linear sales curve to calculate expected internal rate of return for various kinds of drugs. The example results are summarized in the report. I have given considerable thought on how to make this program user friendly and able to handle a basket of drugs in development. I can either do it myself or work with one of your Excel programmers.

- Yet another spread sheet verifying that my simple closed-form version of cash-flow discounting does indeed work.

- A summary booklet of my updated drug discovery course prepared for the University of Maryland.

- Copies of three publications dealing with valuing development stage drugs. I would be interested in seeing what your staff has come up with on this subject.

- Some interesting basic pharmaceutical industry data from PhRMA.

I am quite interested in your approach for understanding market valuation of drugs in development. I think both approaches would make for an interesting publication.

– Lynn Klotz

EXHIBIT 18 KLOTZ 11-16-06 PENGAD 800-631-6989

CONFIDENTIAL
JH 000695

Expected Internal Rate of Return for Investments in Drugs and Development (Using the Linear Model for Sales over Time)

file: lineapp.xl1

This program is to check the closed form vs the year to year calculation cash flow and expected internal rate of return

In all the analyses, in place of dollar units, we will carry out all the analyses in terms of units of potential market; that is the potential market for the drug is 1.0 units. This will standardize the analysis and can be easily converted to dollars by multiplying by market penetration, royalty percentage, investment amount, etc. all in dollars.

Data for example drug:	
Stage of development:	Phase I
prob of launch	prob = 0.2295
years to launch	x0 = 7

Year after product launch to first sale (usually 0 or 1)	xfirst =	1
Year from launch that maximum sales are first reached:	xm =	8
Year from launch that key patents expire:	xp =	10
Year from launch that sales become effectively $0	xend =	20

Calculating discounted sales from the closed-form geometric series formulas

Expected internal rate of return:	Ier =	15.30%
Reciprocal discount factor, v=1/(1+Ier):	v =	0.867334

Ramp up period

Slope of linear curve:	rm =	0.142857
Intercept of linear curve:	rb =	-1.142857
start of sum (beginning of year of first sales):	jj1 =	8
end of sum (first year of maximum sales):	jj2 =	15
Geometric sum:	rGsum =	1.640882
Geometric derivative sum:	rGdsum =	17.67012
Normalized, discounted sales during ramp up period:	rsales =	0.649008

CONFIDENTIAL
JH 000696

Check by calculating discounted sales from individual years

Year after Investment	Year after Launch	Sales Linear Approximation		Discounted Sales
8	1	0		0
9	2	0.142857		0.039681
10	3	0.285714		0.068833
11	4	0.428571		0.089551
12	5	0.571429		0.103561
13	6	0.714286		0.112277
14	7	0.857143		0.116858
15	8	1		0.118248
			TOTAL:	0.649008

The closed and open form of the discounted cash flow agree.

Period of constant, maximum sales

Start of sum (2nd year of constant, maximum sales): jj3 = 16
End of sum (year of patent expiration): jj4 = 17

mGsum = 0.191514

Normalized, discounted sales
during maximum, constant sales period
(not including first year of maximum sales): msales = 0.191514

Check by calculating discounted sales from individual years

Year after Investment	Year after Launch	Linear Approx	Discounted Sales
16	9	1	0.10256
17	10	1	0.088954
	Normalized discounted sales:		0.191514

Both closed and open form agree, so the formulation is OK.

CONFIDENTIAL
JH 000697

Ramp down period after patent expiration

Slope of linear curve:	em =	-0.1000
Intercept of linear curve:	eb =	2.7000
start of sum (beginning of year of first sales):	jj5 =	18
end of sum (first year of maximum sales):	jj6 =	27
Geometric sum:	eGsum =	0.44145
Geometric derivative sum:	eGdsum =	9.431114
Normalized, discounted sales during ramp down period:	esales =	0.248802

Check by calculating discounted sales from individual years

Year after Investment	Year after Launch	Sales Linear Approximation		Discounted Sales
18	11	0.900000		0.069437
19	12	0.800000		0.053534
20	13	0.700000		0.040628
21	14	0.600000		0.030204
22	15	0.500000		0.021831
23	16	0.400000		0.015148
24	17	0.300000		0.009853
25	18	0.200000		0.005697
26	19	0.100000		0.002471
			TOTAL:	0.248802

Both closed and open form agree, so the formulation is OK.

Nales broken down into phases:

ramp up:		0.649008
constant, maximum:		0.191514
ramp down:		0.248802
TOTAL discounted sales:	Tsales =	1.089325

CONFIDENTIAL
JH 000698

Determination of expected internal rate of return

The equation from which we will determine expected internal rate of return is:

p x NPV(er) - I = 0

where p is the probabiity that the return is ever realized (probability that the product is launched)

We will solve the above equation by trial and error using the Excel Solver function
to find the er which satisfies the equation.

Potential market (millions):	PM = $	500
Market penetration	penet =	40%
Investor's royalty rate	Royalty =	10%

Since the sales curve is normalized to 1.0 potential market, we need also to normalize
the investment IV to the 1.0 unit potential market

Investment (millions)	IV= $	5.00
investment normalized to potential market	NIV=	0.0100

Normalized discounted sales:	Tsales =	1.089325
Normalized net present value of return on investment:	nNPV=	0.043573

Expected net present value prob x LNPV	ELNPV =	0.01000
Normalized investment	NIV =	0.0100
Expected internal rate of return (OTA) (based on solving: prob x LNPV - NIV =0):	Ier =	15.30%
Check on solver solution:	p x LNPV - NIV =	2.33E-10

***either this answer is correct or the 15,34% found earlier is correct.
Probabably one extra year was included in the discounting so look at jjx limits.
and if need be do the brute force check of listing all the years

CONFIDENTIAL
JH 000699

CONFIDENTIAL

Expected Internal Rate of Return

file: eirr#3.wpd v. 4/12/00

Introduction

The internal rate of return (IRR) is a better function than net present value (NPV) for evaluating investments with future cash flow because it makes no assumptions about discount rates. Instead, IRR yields the rate of return on a potential investment. If the rate of return is acceptable then the investment can be made. In contrast, to calculate NPV for a potential investment, a discount rate must be assumed.

Both the standard NPV and IRR methods for evaluating potential investments make the critical assumption that future cash flows will be realized with certainty. In the case of drugs in development, there is a good chance the drug will never reach the marketplace, in which case the future cash flows will never be realized. Fortunately for drugs in development, a reasonable set of probabilities and time-lines have been determined for an average drug to reach the marketplace depending on its stage of development. For this situation, the standard expectation function is now the appropriate way of calculating expected return, and discounting of cash flows would begin in the year that sales commence. The internal rate of return that takes into account probabilities that a drug may never reach the marketplace, we dub expected internal rate of return (EIRR).

For a particular drug, there are a number of factors with will affect the dollar-magnitude and shape of the cash flow curve over the years. Specifically,

- The potential market for the drug.
- Market penetration for the drug.
- Years from the point of investment to first sales. This depends on the stage of development of the drug (e.g., stage of clinical trials when the investment is made).
- Years from the point of investment until maximum sales are reached. Drugs for very serious or fatal or expensive conditions such as sickle cell anemia, cystic fibrosis and AIDS can ramp up to maximum sales within a year or two. In contrast, drugs for less serious conditions, such as mild asthma, may take several years to fully penetrate the market.
- Years from the point of investment to expiration of key patents protecting the drug.

Each of these factors can affect significantly NPV, EIRR or any financial measure of investment worthiness for a development-stage drug. For NPV, for example, at a high 40% discount rates typical employed for high risk investments, an error in estimation of even two years to significant sales can make a factor of two difference in the value of the investment ($1.40^2=1.96$). Thus, it is especially important that we estimate as accurately as possible the occurrence over time of the various events discussed above.

CONFIDENTIAL
JH 000700

CONFIDENTIAL

For an investment that bears royalties based on future cash flows, we need to know the profile of sales over time. Several years ago the now-defunct US agency, the Office of Technology Assessment, traced 100 drugs over 32 years from development to the marketplace, and through their years of sales (See Figure 1). This sales vs time profile has been widely adopted to calculate NPV sales for "average" drugs. To account for the fact that many drugs deviate significantly from this average profile, we propose here to account for drugs with different cash-flow properties (discussed in the above bulleted points) by using three linear functions to approximate sales profiles over time:

(1) A linear ramp up in sales from FDA approval to maximum sales;
(2) A flat linear function representing maximum sales until key patents expire; and
(3) A linear decrease in sales after patents expire.

The three-lines approximating the OTA sales data is presented graphically in Figure 2. To demonstrate the precision with which this *three-linear approximation* can estimate EIRR, it was first used to estimate cash flow from the OTA profile for average drugs. Finally, EIRR is determined for drugs with different ramp-up, flat sales, and ramp-down profiles to illustrate the importance of profile on EIRR.

Example Results

In Table 1 below comparisons of the three-linear approximation with the OTA sales profile are presented for drugs in preclinical phase and phases I, II and III clinical trials. For the results presented in the Table, the probabilities and time lines are those presented by Ashley Stevens for typical large company new chemical entities (NCE). For each drug, the following financial data was assumed: a potential market of $500 million; market penetration of 40%; and an investment of $5 million. Only royalty rate was varied to yield expected internal rates of return between 10% and 20% for each case.

As indicated in Table 1, the three-linear approximation agrees well with the internal rate of return for the OTA Sales Profile. The nearly constant difference between the two (about 0.8%) holds even for internal rates of return well below 10%. For EIRR's around 15%, the three-linear approximation is only 6% different from the OTA profile, which is more than acceptable for these kinds of calculations. Furthermore, the royalty rate that the investor should receive to realize an acceptable EIRR (15% or greater) on the $5 million investment of this example is greatly dependent on the stage of drug development, ranging from 20% to 2%.

CONFIDENTIAL
JH 000701

CONFIDENTIAL

Table 1. Comparison of Expected Internal Rate of Return Calculated Using the OTA Sales-Over-Time Profile with its Three-Linear Approximation[1]

Phase of Drug Development	Probability Drug Reaches Marketplace[1]	Years to Market Launch[2]	Assumed Royalty Rate	EIRR from OTA Profile	EIRR from Three-Linear Approxi-mation
Preclinical	0.115	9	20%	14.1%	13.4%
Phase I	0.230	7	10%	16.1%	15.3%
Phase II	0.306	6	8%	17.8%	17.0%
Phase III	0.638	4	2%	14.7%	13.8%

1. In all cases, the following financial data was used: a potential market of $500 million; market penetration of 40%; and an investment of $5 million.
2. The probabilities are for drugs in each phase of development; where in the phase is unspecified.
3. In these examples, it was assumed that first sales did not occur until one year after launch, which is consistent with the OTA curve.

In Table II below the ramp-up rate, length of constant sales period and rate of declining sales are varied to illustrate importance of these sales characteristics on internal rate of return. It is clear from the data in Table 2 that the kind of drug--typical or fast-tracked--will have a significant effect on expected internal rate of return, with greater effect on drugs nearer product launch (Phase III).

CONFIDENTIAL
JH 000702

CONFIDENTIAL

Table 2. Illustration of Importance of Sales Curve Characteristics on Expected Internal Rate of Return[1]

Type of Drug[2] (EIRR)[3]	Clinical Trial Phase	Years from Launch to First Sale	Years from Launch to Maximum Sales	Years from Launch to Expiration of Key Patents	Years from Launch to End of All Sales
Typical Drug (15.3%)	Phase I	1	8	10	20
Fast-tracked Drug (20.7)	Phase I	0	2	10	20
Typical Drug (13.8)	Phase III	1	8	10	20
Fast-tracked Drug (20.4)	Phase III	0	2	10	20

1. In both cases, the following financial data was used: a potential market of $500 million; market penetration of 40%; and an investment of $5 million.
2. For the two drugs in Phase I, the probability that it will reach the marketplace is 0.230 and 7 years to product launch.and royalty rate of 10%. For the two drugs in Phase III, the probability that it will reach the marketplace is 0.638 and 4 years to product launch.and royalty rate of 2%.
3. The expected internal rate of return calculated for each drug development case is in parentheses

Overview of Mathematical Approach

The internal rate of return (IRR) is a better function than net present value (NPV) for evaluating investments with future cash flow because it makes no assumptions about discount rates. Instead, IRR yields the rate of return on a potential investment. If the rate of return is acceptable then the investment can be made. In contrast, to calculate NPV for a potential investment, a discount rate must be assumed.

CONFIDENTIAL
JH 000703

CONFIDENTIAL

In mathematical terms, for a series of future cash flows CF_y paid out at the end of years y, the NPV is a function of the discount rate, d:

$$NPV(d) = CF_1/(1+d)^1 + CF_2/(1+d)^2 + \ldots + Cf_n/(1+d)^n = \sum_{y=1}^{n} Cf_y/(1+d)^y \quad (1)$$

where n is the last year of cash flow.

In the case of drugs in development, the cash flow usually does not begin until some year in the future, so the sum in equation (1) is more generally written:

$$NPV(d) = CF_a/(1+d)^a + CF_{a+1}/(1+d)^{a+1} + \ldots + Cf_n/(1+d)^n = \sum_{y=a}^{n} Cf_y/(1+d)^y \quad (2)$$

where a is the first year of cash flow.

For an initial investment I, the internal rate of return is defined as the discount rate r that yields an NPV exactly equal to the intial investment. Explicitly,

$$NPV(r) = I \quad (3)$$

or

$$NPV(r) - I = 0 \quad (4)$$

For a series of yearly cash flows CF_y that do not obey a simple function of y, IRR must be found by trial and error, that is, by substituting various discount rates d until the discount rate r is found for which equations (3) or (4) are obeyed. With the Excel spread sheet the "Solver" function allows for this trial-and-error task to be accomplished in a few seconds. In cases where the CF_y vary in some simple fashion over years (e.g., constant over years or varies linearly over years), a simple equation for r can sometimes be derived to eliminate the trial and error estimation procedure.

Both the standard NPV and IRR methods for evaluating potential investments make the critical assumption that future cash flows will be realized with certainty. In the case of drugs in development, there is a good chance the drug will never reach the marketplace, in which case the future cash flows will never be realized. Fortunately for drugs in development, a reasonable set of probabilities and time-lines have been determined for an average drug to reach the marketplace depending on its stage of development.

CONFIDENTIAL

For this situation, let p be the probability that the drug reaches the marketplace and the discounted future cash flow is realized. then 1-p is the probability that the drug fails to reach the marketplace and no cash flow is realized. The standard expectation function is the appropriate way of calculating expected return. Therefore, define an *expected net present value* for discount rate d as

$$E(d) = p \times NPV(d) - (1-p) \times 0 = p \times NPV(d) \tag{5}$$

(Note when p=1 where return is certain E(d) is just the standard NPV which is correct, and when p=0 where no return is ever realized. E(d) = 0 indicating no return on the investment which is also correct.)

Further define an *expected internal rate of return* (EIRR) as the discount rate, er, that makes E(d) equal to the investment. Specifically,

$$p \times NPV(er) - I = 0 \tag{6}$$

As with IRR, EIRR must be evaluated by trial and error except in special cases where the yearly cash flows follow a simple yearly function.

The discount rate, er, found from equation (6) is the mathematically proper way of evaluating cash flows where there is some probability 1-p that the return will never be realized.

For an investment, I, in a basket of drugs, we may define the *total expected net present value*, T(d), as the sum for each drug. Specifically for j=1.,2....J drugs each with a probability of p_j of reaching the market place and each with a net present vlaue of $NPV_j(d)$, the total expected net present value is given by

$$T(d) = p_1NPV_1(d) - p_2NPV_2(d) + p_3NPV_3(d) + ... + p_2NPV_4(d) \tag{7}$$

EIRR is then the discount rate, er, that satisfies the following equation:

$$T(er) - I = 0 \tag{8}$$

For a particular drug, there are a number of factors that will affect the dollar-magnitude and shape of the cash flow curve CF_y vs y over the years. Specifically,

- The potential market for the drug.
- Market penetration for the drug.
- Years from the point of investment to first sales. This depends on the stage of development of the drug (e.g., stage of clinical trials when the investment is made).
- Years from the point of investment until maximum sales are reached. Drugs for very serious or fatal or expensive conditions such as sickle cell anemia, cystic fibrosis and AIDS

can ramp up to maximum sales within a year or two as they are desperately needed. In contrast, drugs for less serious conditions, such as mild asthma, may take several years to fully penetrate the market.

- Years from the point of investment to expiration of key patents protecting the drug.

Each of these factors can affect significantly the NPV, EIRR or any financial measure of investment worthiness for a development-stage drug. For NPV, for example, at a high 40% discount rates typical of high risk investments, an error in estimation of even two years to significant sales can make nearly a factor of two difference in the value of the investment ($1.40^2=1.96$). Thus, it is especially important that we estimate as accurately as possible the occurrence over time of the various events discussed above.

For an investment that bears royalties based on future cash flows, we need to know the profile of sales over time. Several years ago the now-defunct US agency, the Office of Technology Assessment. traced 100 drugs over 32 years from development, to the marketplace, and through their years of sales (See Figure 1). This cash flow profile has been widely adopted to calculate NPV sales for "average" drugs. To account for the fact that many drugs deviate significantly from this average profile, we propose here to account for different cash-flow profiles (the above bulleted points) by using three linear functions to approximate sales over time:

(1) A linear ramp up in sales from FDA approval to maximum sales;
(2) A flat linear function representing maximum sales until key patents expire; and
(3) A linear decrease in sales after patents expire.

To test the precision this *three-linear approximation* estimates EIRR, it first will be compared to EIRR calculated from the OTA profile for average drugs. Finally, EIRR will be calculated for drugs with different ramp-up. flat sales, and ramp-down profiles to illustrate the importance of profile on EIRR.

To simplify the calculation task for the three-linear approximation, values of NPV(d) needed to calculate EIRR can be expressed in three closed-form analytic formulae. These closed-form formulae can each be programmed into *one or two* spread-sheet cells; thereby greatly simplifying the calculation task which usually involves listing the cash flow for each future year, discounting each year's cash flow, and then adding the result. The derivations of the closed-form formulae based on the geometric series and its first derivative are presented in Appendix I, and the results are summarized below.

Equation (6) can be rewritten in closed form as

$$mv^a[v \times dS_{n-a}(v)/dv + a\, S_{n-a}(v)] + bv^a\, S_{n-a}(v) = I/p \qquad (9)$$

where $dS_{n-a}(v)/dv$ and $S_{n-a}(v)$ are given by:

CONFIDENTIAL

$$S_{n-a}(v) = (1 - v^{n-a-1})/(1-v) \quad (10)$$

$$dS_{n-a}(v)/dv = [1-v^{n-a-1}-(1-v)(n-a+1)v^{n-a}]/(1-v)^2 \quad (11)$$

where m and b are the slope and intercept of the linear cash flow, and

$$v = 1/(1+er) \quad (12)$$

For any linearly increasing or decreasing cash flow over time, equation (9) is solved by varying v (using trial and error) until the equation is satisfied, then the expected internal rate of return, er, is simply found by inverting equation (11):

$$er = (1-v)/v \quad (13)$$

Note also that the expression in the left hand side of equation (9) is just the net present value of the cash flow for any discount rate d:

$$NPV(d) = mv(d)^a[v(d) \times dS_{n-a}(v(d))/dv + a\, S_{n-a}(v(d))] + bv(d)^a S_{n-a}(v(d)) \quad (14)$$

and

$$v(d) = 1/(1+d) \quad (15)$$

Therefore, equation (14) can be used to calculate quickly the NPV for any linear cash flow with any interest rate d.

For a typical drug sales curve where there is:

- A linear ramp-up phase beginning at year j1 and ending at year j2 with slope m_r and intercept b_r,
- A constant maximum sales phase beginning at year j2+1 and ending at year j3 with slope m_c=0 and intercept b_c; and
- A declining sales phase beginning at year j3+1 and ending at year j4 with slope m_d and intercept b_d, then

the total NPV is just the sum of the three linear profiles.

CONFIDENTIAL
JH 000707

CONFIDENTIAL

Appendix I. Derivation of a closed-form expression for internal rate of return for linear cash flow.

The expected internal rate of return is given by equation (6)

$$p \times NPV(er) - I = 0 \qquad \text{(i)}$$

Rearranging gives

$$NPV(er) = I/p \qquad \text{(ii)}$$

Substituting for NPV in terms of cash flows, equation (2) from the main text:

$$\sum_{y=a}^{n} CF_y/(1+er)^y = I/p \qquad \text{(iii)}$$

where a is the year in which the linear cash flow begins and n is the year that it ends.

Now we can make a simplifying substitution to make the sum in equation (iii) look more like the geometric series that it is. Let

$$v = 1/(1+er) \qquad \text{(iv)}$$

Then

$$1/(1+er)^y = [1/(1+er)]^y = v^y \qquad \text{(v)}$$

Equation (iii) may now be rewritten

$$\sum_{y=a}^{n} CF_y \times v^y = I/p \qquad \text{(vi)}$$

For a cash flow that increases or decreases linearly over the years

$$CF_y = my + b \qquad \text{(vii)}$$

where m and b are, respectively, slope and intercept of the straight line.

Substituting this linear relationship into equation (vi) yields

CONFIDENTIAL
JH 000708

CONFIDENTIAL

$$\sum_{y=a}^{n} (my + b) \times v^y = I/p \qquad \text{(viii)}$$

which may be rewritten as

$$mv^a \sum_{y=0}^{n-a} (y+a) \times v^y + bv^a \sum_{y=0}^{n-a} v^y = I/p \qquad \text{(ix)}$$

These two sums can be put into closed form using the closed form of the geometric series. The sum of the first n-a terms of a geometric series $S_{n-a}(v)$ may be written in open and closed form as:

$$S_{n-a}(v) = 1 + v + v^2 - v^3 + v^3 + \ldots + v^{n-a} = \sum_{y=0}^{n-a} v^y = (1 - v^{n-a+1})/(1-v) \qquad \text{(x)}$$

so equation (ix) becomes:

$$mv^a[\sum_{y=0}^{n-a} y \times v^y + aS_{n-a}(v)] + bv^a S_{n-a}(v) = I/p \qquad \text{(xi)}$$

The remaining sum in equation (xi) may be expressed in closed form using the derivative with respect to v of the geometric series of equation (x) as follows:

$$dS_{n-a}(v)/dv = 0 + 1 - 2v + 3v^2 + 4v^3 + \ldots + (n-a)v^{n-a-1} \qquad \text{(xii)}$$

Multiplying this derivative by v gives exactly the sum in equation (xi):

$$v \times dS_{n-a}(v)/dv = v - 2v^2 + 3v^3 + 4v^4 + \ldots + (n-a)v^{n-a} \qquad \text{(xiii)}$$

which may be expressed in closed form by evaluating

$$v \times dS_{n-a}(v)/dv = v \times d\,[\,(1 - v^{n-a+1})/(1-v)]/dv \qquad \text{(xiv)}$$

Evaluating the derivative and simplifying gives

$$v \times dS_{n-a}(v)/dv = v \times [1-v^{n-a+1}-(1-v)(n-a+1)v^{n-a}]/(1-v)^2 \qquad \text{(xv)}$$

Equation (ix) may therefore be rewritten as

CONFIDENTIAL
JH 000709

CONFIDENTIAL

$$mv^a[v \times dS_{n-a}(v)/dv + a\, S_{n-a}(v)] + bv^a S_{n-a}(v) = I/p \qquad \text{(xvi)}$$

where the closed form for the geometric series related terms are again:

$$S_{n-a}(v) = (1 - v^{n-a-1})/(1-v) \qquad \text{(xvii)}$$

and

$$dS_{n-a}(v)/dv = [1-v^{n-a-1}-(1-v)(n-a+1)v^{n-a}]/(1-v)^2 \qquad \text{(xviii)}$$

Although this last expression is a bit cumbersome, it will nevertheless fit into a single cell on a spreadsheet.

Expected Internal Rate of Return for Investments in Drugs and Development

file: ota-lin.xl1

In all the analyses, in place of dollar units, we will carry out all the analyses in terms of units of potential market; that is the potential market for the drug is 1.0 units. This will standardize the analysis and can be easily converted to dollars by multiplying by potential market, investment amount, etc. all in dollars.

The Office of Technology Assessment's (OTA) sales curve normalized to maximum sales of 1.0 units is given below:

Years after product launch	Normalized OTA sales	Linear OTA Approximation
1	0	0
2	0.125	0.142857
3	0.297	0.285714
4	0.422	0.428571
5	0.766	0.571429
6	0.844	0.714286
7	0.922	0.857143
8	1	1
9	1	1
10	1	1
11	0.922	0.9
12	0.937	0.8
13	0.859	0.7
14	0.781	0.6
15	0.703	0.5
16	0.578	0.4
17	0.422	0.3
18	0.266	0.2
19	0.125	0.1
20	0	0

UPM = 11.969 **LUPM =** **10.5** (undiscounted total possible sales)

CONFIDENTIAL
JH 000711

The probability that a drug is launched into the marketplace (sales occur)
as a function of stage of development and type of drug:

For biotechnology drugs:
(from Stevens, Table 13 and Nicholson and Latham, Table 2)

Stage of development	Probability of launch	Years to product launch
preclinical	0.352096	6
phase I	0.664332	4
phase II	0.7636	3
phase III	0.92	2
NDA filed	1	1
approval/launch	1	0

For NCE's from large pharma
(from Stevens, Table 10)

Stage of development	Probability of launch	Years to product launch
preclinical	0.11475	
phase I	0.2295	7
phase II	0.306	6
phase III	0.6375	4
NDA filed	0.85	2
approval/launch	1	0

The equation from which we will determine expected internal rate of return is:

p x NPV(er) - I = 0

where p is the probabiity that the return is ever realized (probability that the product is launched)

We will solve the above equation by trial and error (or Excel Solver function)
to find the er which satisfies the equation.

CONFIDENTIAL
JH 000712

As an example for an average big company NCE:

Stage of development:			Phase I
prob of launch	p =		0.2295
years to launch	y0 =		7
Potential market (millions):	PM=	$	500
Market penetration	penet=		40%
Investor's royalty rate	R=		10%

Since the sales curve is normalized to 1.0 potential market, we need also to normalize the investment IV to the 1.0 unit potential market

Investment (millions)	IV=	$	5.00
investment normalized to potential market	NIV=		0.0100

CONFIDENTIAL
JH 000713

Trial and error determination of er

The investor' discounted return below takes into account market penetration and royalty rate to the investor.

Years after product launch	Normalized OTA sales	Investor's Discounted Return (OTA)	Linear OTA Approximation	Investor's Discounted Return (lin)
1	0	0	0	0
2	0.125	0.00131	0.142857	0.001587
3	0.297	0.002682	0.285714	0.002753
4	0.422	0.003283	0.428571	0.003582
5	0.766	0.005136	0.571429	0.004142
6	0.844	0.004876	0.714286	0.004491
7	0.922	0.00459	0.857143	0.004674
8	1	0.00429	1	0.00473
9	1	0.003697	1	0.004102
10	1	0.003185	1	0.003558
11	0.922	0.002531	0.9	0.002777
12	0.937	0.002216	0.8	0.002141
13	0.859	0.001751	0.7	0.001625
14	0.781	0.001372	0.6	0.001208
15	0.703	0.001064	0.5	0.000873
16	0.578	0.000754	0.4	0.000606
17	0.422	0.000474	0.3	0.000394
18	0.266	0.000258	0.2	0.000228
19	0.125	0.000104	0.1	9.88E-05
20	0	0	0	0

Normalized net present value	NPV =	0.043573	LNPV=	0.043573
Expected net present value	ENPV =	0.01	LENPV=	0.01

CONFIDENTIAL
JH 000714

Example results comparing OTA sales curve with its linear approximation

A big company NCE

Stage of development:		Phase I
prob of launch	p =	0.2295
years to launch	y0 =	7
Potential market (millions):	PM= $	500
Market penetration	penet=	40%
Investor's royalty rate	R=	10%

Since the sales curve is normalized to 1.0 potential market, we need also to normalize the investment IV to the 1.0 unit potential market

Investment (millions)	IV= $	5.00
investment normalized to potential market	NIV=	0.0100

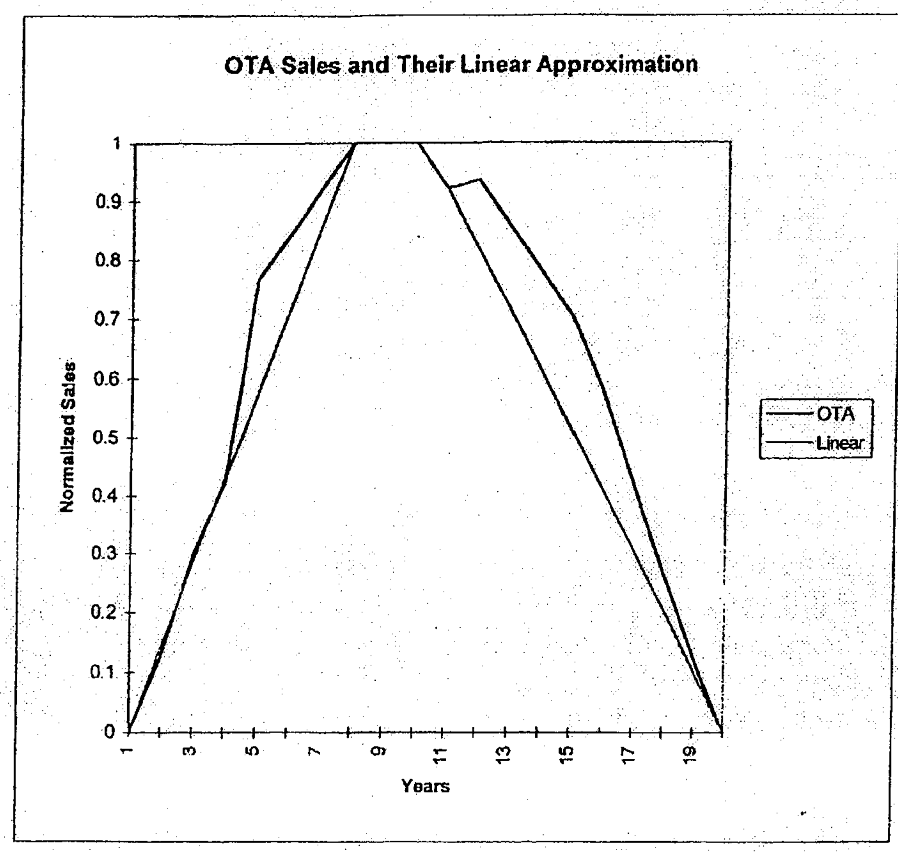
	OTA		Linear Approx	
Normalized net present value:	NPV =	0.0436	LNPV =	0.0436
Expected net present value p x (net present value):	ENPV =	0.010	LENPV =	0.0100

er = 16.05%
ler = 15.30%

p x NPV - NIV = -5.6E-08
p x LNPV - NIV = 6.93E-13

CONFIDENTIAL
JH 000715

Years	OTA	Linear
1	0	0
2	0.125	0.142857
3	0.297	0.285714
4	0.422	0.428571
5	0.766	0.571429
6	0.844	0.714286
7	0.922	0.857143
8	1	1
9	1	1
10	1	1
11	0.922	0.922
12	0.937	0.819556
13	0.859	0.717111
14	0.781	0.614667
15	0.703	0.512222
16	0.578	0.409778
17	0.422	0.307333
18	0.266	0.204889
19	0.125	0.102444
20	0	0



CONFIDENTIAL
JH 000717

Example results comparing OTA sales curve with its linear approximation

A big company NCE

Stage of development:		Preclinical
prob of launch	p =	0.11475
years to launch	y0 =	9
Potential market (millions):	PM=	$ 500
Market penetration	penet=	40%
Investor's royalty rate	R=	20%

Since the sales curve is normalized to 1.0 potential market, we need also to normalize the investment IV to the 1.0 unit potential market

Investment (millions)	IV=	$ 5.00
investment normalized to potential market	NIV=	0.0100

	OTA		Linear Approx	
Normalized net present value:	NPV =	0.0871	LNPV =	0.0871
Expected net present value p x (net present value):	ENPV =	0.010	LENPV =	0.0100

er =	14.05%
ler =	13.39%

p x NPV - NIV =	1.36E-10
p x LNPV - NIV =	-2.6E-10

CONFIDENTIAL
JH 000718

Example results comparing OTA sales curve with its linear approximation

A big company NCE

Stage of development:		Phase I
prob of launch	p =	0.2295
years to launch	y0 =	7
Potential market (millions):	PM= $	500
Market penetration	penet=	40%
Investor's royalty rate	R=	10%

Since the sales curve is normalized to 1.0 potential market, we need also to normalize the investment IV to the 1.0 unit potential market

Investment (millions)	IV= $	5.00
investment normalized to potential market	NIV=	0.0100

	OTA		Linear Approx	
Normalized net present value:	NPV =	0.0436	LNPV =	0.0436
Expected net present value p x (net present value):	ENPV =	0.010	LENPV =	0.0100

er = 16.05%
ler = 15.30%

p x NPV - NIV = -8.5E-10
p x LNPV - NIV = -2.3E-09

CONFIDENTIAL
JH 000719

Example results comparing OTA sales curve with its linear approximation

A big company NCE

Stage of development:			Phase III
prob of launch	p =		0.6375
years to launch	y0 =		4
Potential market (millions):	PM=	$	500
Market penetration	penet=		40%
Investor's royalty rate	R=		2%

Since the sales curve is normalized to 1.0 potential market, we need also to normalize the investment IV to the 1.0 unit potential market

Investment (millions)	IV=	$	5.00
investment normalized to potential market	NIV=		0.0100

	OTA		Linear Approx	
Normalized net present value:	NPV =	0.0157	LNPV =	0.0157
Expected net present value p x (net present value):	ENPV =	0.010	LENPV =	0.0100

er =	14.70%
ler =	13.77%

p x NPV - NIV =	3.62E-09
p x LNPV - NIV =	-7.6E-10

CONFIDENTIAL
JH 000720

Expected Internal Rate of Return for Investments in Drugs and Development
(Using the Linear Model for Sales over Time)

file: linear.xl1

This program is designed to calculate expected internal rates of return in terms of units of potential market; that is, the potential market for the drug is normalized to 1.0 units. This will standardize the analysis and can be easily converted to dollars by multiplying by market penetration, royalty percentage, investment amount, etc. all in dollars.

Input information

Data for development stage drug:

Stage of development:	Phase I
prob of launch	prob = 0.2295
years to launch	x0 = 7

Year after product launch to first sale (usually 0 or 1)	xfirst =	1
Year from launch that maximum sales are first reached:	xm =	8
Year from launch that key patents expire:	xp =	10
Year from launch that sales become effectively $0	xend =	20

Market/investment information

Potential market (millions):	PM =	$	500
Market penetration	penet =		40%
Investor's royalty rate	Royalty =		10%
Investment (millions)	IV=	$	5.00

Results: expected internal rate of return, Ier, and other discounted quantities of interest:

Expected internal rate of return:
(based on solving: prob x nNPV - NIV =0): Ier = 15.30%

Normalized discounted sales broken down into phases:

ramp up:		0.649008
constant, maximum:		0.191514
ramp down:		0.248802
TOTAL discounted sales:	Tsales =	1.089325

Normalized net present value of
return on investment (penet*RR*Tsales): nNPV= 0.043573

Expected net present value in millions of dollars:
which must equal initial investment (prob x nNPV x PM): $ 5.00

CONFIDENTIAL
JH 000721

Determination of expected internal rate of return

The equation for determining expected internal rate of return is: prob x NPV(Ier) - I = 0
where p is the probability that the return is ever realized (probability that the product is launched)
The above equation is solved by trial and errror using the Excel Solver function
to find the expected internal rate of return, Ier, which satisfies the equation.

Normalizing the investment, IV, to the 1.0 unit potential market:

Investment (millions)	IV=	$ 5.00
Investment normalized to potential market	NIV=	0.0100
Normalized discounted sales:	Tsales =	1.089325
Normalized net present value of return on investment (penet*RR*Tsales):	nNPV=	0.043573
Expected net present value prob x nNPV	ELNPV =	0.01000
Expected internal rate of return (based on solving: prob x nNPV - NIV =0):	Ier =	15.30%

to use Excel "Solver" function to find Ier, the target cell is the cell after the equals sign in the equation below and the solution is obtained by changing Ier:

Check on solver solution: p x LNPV - NIV = -4.1E-11

CONFIDENTIAL
JH 000722

Details of obtaining the closed form solution

The geometric series factor v=1/(1+ler):	v =	0.867334

Ramp up period

Slope of linear curve:	rm =	0.142857
Intercept of linear curve:	rb =	-1.142857
start of sum (beginning of year of first sales)	jj1 =	8
end of sum (first year of maximum sales):	jj2 =	15
Geometric sum:	rGsum =	1.640882
Geometric derivative sum:	rGdsum =	17.67012
Normalized, discounted sales during ramp up period:	rsales =	0.649008

Period of constant, maximum sales

Start of sum (2nd year of constant, maximum sales):	jj3 =	16
End of sum (year of patent expiration):	jj4 =	17
	mGsum =	0.191514
Normalized, discounted sales during maximum, constant sales period (not including first year of maximum sales):	msales =	0.191514

CONFIDENTIAL
JH 000723

Ramp down period after patent expiration

Slope of linear curve:	em =	-0.1000
Intercept of linear curve:	eb =	2.7000
start of sum (beginning of year of first sales)	jj5 =	18
end of sum (first year of maximum sales):	jj6 =	27
Geometric sum:	eGsum =	0.44145
Geometric derivative sum:	eGdsum =	9.431113
Normalized, discounted sales during ramp down period:	esales =	0.248802

Normalized discounted sales broken down into phases:

ramp up:		0.649008
constant, maximum:		0.191514
ramp down:		0.248802
TOTAL discounted sales:	Tsales =	1.089325

CONFIDENTIAL
JH 000724

Tables of probability and years to launch information for drugs in development

For biotechnology drugs:
(from Stevens, Table 13 and Nicholson and Latham, Table 2)

Stage of development	Probability of launch	Years to product launch
preclinical	0.352096	6
phase I	0.664332	4
phase II	0.7636	3
phase III	0.92	2
NDA filed	1	1
approval/launch	1	0

For NCE's from large pharma
(from Stevens, Table 10)

Stage of development	Probability of launch	Years to product launch
preclinical	0.11475	
phase I	0.2295	7
phase II	0.306	6
phase III	0.6375	4
NDA filed	0.85	2
approval/launch	1	0

CONFIDENTIAL
JH 000725

Expected Internal Rate of Return for Investments in Drugs and Development
(Using the Linear Model for Sales over Time)

file: linear.xl1

This program is designed to calculate expected internal rates of return in terms of units of potential market; that is, the potential market for the drug is normalized to 1.0 units. This will standardize the analysis and can be easily converted to dollars by multiplying by market penetration, royalty percentage, investment amount, etc. all in dollars.

Input information

Data for development stage drug:

Stage of development:	Phase I	
prob of launch	prob =	0.2295
years to launch	x0 =	7

Year after product launch to first sale (usually 0 or 1)	xfirst =	0
Year from launch that maximum sales are first reached:	xm =	2
Year from launch that key patents expire:	xp =	10
Year from launch that sales become effectively $0	xend =	20

Market/investment information

Potential market (millions):	PM =	$ 500
Market penetration	penet =	40%
Investor's royalty rate	Royalty =	10%
Investment (millions)	IV=	$ 5.00

Results: expected internal rate of return, Ier, and other discounted quantities of interest:

Expected internal rate of return:
(based on solving: prob x nNPV - NIV =0): Ier = 20.67%

Normalized discounted sales broken down into phases:

ramp up:		0.29557
constant, maximum:		0.693488
ramp down:		0.100266
TOTAL discounted sales:	Tsales =	1.089324

Normalized net present value of
return on investment (penet*RR*Tsales): nNPV= 0.043573

Expected net present value in millions of dollars:
which must equal initial investment (prob x nNPV x PM): $ 5.00

CONFIDENTIAL
JH 000726

Expected Internal Rate of Return for Investments in Drugs and Development
(Using the Linear Model for Sales over Time)

file: linear.xl1

This program is designed to calculate expected internal rates of return in terms of units of potential market; that is, the potential market for the drug is normalized to 1.0 units. This will standardize the analysis and can be easily converted to dollars by multiplying by market penetration, royalty percentage, investment amount, etc. all in dollars.

Input information

Data for development stage drug:

Stage of development:	Phase II	
prob of launch	prob =	0.306
years to launch	x0 =	6

Year after product launch to first sale (usually 0 or 1)	xfirst =	0
Year from launch that maximum sales are first reached:	xm =	2
Year from launch that key patents expire:	xp =	10
Year from launch that sales become effectively $0	xend =	20

Market/investment Information

Potential market (millions):	PM =	$	500
Market penetration	penet =		40%
Investor's royalty rate	Royalty =		10%
Investment (millions)	IV=	$	5.00

Results: expected internal rate of return, Ier, and other discounted quantities of interest:

Expected internal rate of return:
(based on solving: prob x nNPV - NIV =0): Ier = 26.05%

Normalized discounted sales broken down into phases:

ramp up:		0.255818
constant, maximum:		0.50787
ramp down:		0.053305
TOTAL discounted sales:	Tsales =	0.816993

Normalized net present value of
return on Investment (penet*RR*Tsales): nNPV= 0.03268

Expected net present value in millions of dollars:
which must equal initial investment (prob x nNPV x PM): $ 5.00

CONFIDENTIAL
JH 000727

KLOTZ DEPOSITION EXHIBIT 19

D'S EXHIBIT 807 – PART 1

CONFIDENTIAL

ABT – 773

Descriptive Memorandum

February 2001

Abbott Laboratories

PENGAD 800-631-6989
EXHIBIT
19

CONFIDENTIAL
JH 008153

ABT-773

Opportunity Overview

ABT-773 pertains to a promising new class of antibiotics known as ketolides. ABT-773 is likely to have activity against resistant strains of bacteria and will, therefore, compete effectively against currently marketed antibiotics. The compound is currently in Phase II/III trials. Phase III clinical trials began in Q4, 2000. ABT-773 has an expected U.S. launch date in Q1, 2004. Ex-U.S. launches are projected in 2004 for Europe and Japan.

Product features such as high efficacy, activity against resistant strains of bacteria and convenience should enable it to compete against both Zithromax and newer agents such as the quinolones. Dosing is expected to be once-a-day. A 5-day convenience pak at a competitive price will help maximize sales.

The US Market

The overall antibiotic market in the U.S. reached $8.9 billion in sales in 1999. The tab/cap segment is the largest; sales in 1999 were $5.7 billion. The I.V. and oral suspension segments are comparatively smaller; total sales topped $2.1 and $1.1 billion, respectively.

Tab/cap and oral suspension prescription volume had been declining 1-2% per year in the period of 1995-1998, due to more appropriate prescribing in the face of increasing resistance. However, total tab/cap prescription volume recovered in 1999 and grew 6.3%. Even in the face of negative pressure on antibiotic use, dollar sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics. The market is willing to bear higher costs for agents that satisfy unmet needs. The I.V. market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

Macrolides, largely fueled by the gains of Zithromax, have seen significant growth in terms of both prescriptions and sales. Zithromax prescriptions far outnumber those of other competitors, while its sales have nearly surpassed those of the sales leader, Cipro. Historically, quinolones saw relatively limited use for community respiratory tract infections (RTIs) because of poor Gram-positive coverage and sub-optimal adverse event profiles. Newer quinolones such as Levaquin have been successful in achieving more widespread use by virtue of its improved activity and adverse event profile. Levaquin currently accounts for approximately 30% of the quinolone market share. It is anticipated that recent quinolone introductions (Avelox, Tequin) will build upon the RTI momentum established by Levaquin. The growth of the macrolide and quinolone classes has come largely at the expense of cephalosporins and generic agents such as erythromycin and penicillin.

The following table shows 1999 tab/cap sales and prescriptions by class/product:

	Sales			TRXs		
	Sales ($MM)	Share	$CAGR_{95-99}$	TRXs (MM)	Share	$CAGR_{95-99}$
Penicillins	$148.3	2.6%	-1.0%	52.5	23.7%	-5.6%
Cephalosporins	$980.9	17.2%	-5.8%	37.9	17.1%	-3.5%
Ceftin	$383.9	6.7%	1.8%	5.0	2.3%	-1.0%
Cefzil	$188.7	3.3%	12.5%	2.7	1.2%	11.3%
Other	$408.3	7.1%	-14.7%	30.1	13.6%	-4.8%
Ext. Spec. Macrolides	$1,595.6	27.9%	19.9%	36.1	16.3%	20.8%
Biaxin	$690.5	12.1%	6.1%	11.3	5.1%	1.2%
Zithromax	$891.1	15.6%	42.1%	24.4	11.0%	41.5%
Other	$14.0	0.2%	21.0%	0.4	0.2%	53.0%
Quinolones	$1,622.1	28.4%	17.0%	24.0	10.8%	11.7%
Cipro	$902.5	15.8%	8.3%	14.1	6.4%	5.1%
Levaquin	$529.4	9.3%	NA	7.0	3.1%	NA
Other	$190.2	3.3%	-2.2%	3.0	1.3%	-6.4%
Augmentin	$778.1	13.6%	17.8%	10.7	4.8%	11.8%
Other Classes	$590.5	10.3%	-1.1%	60.4	27.3%	-4.1%
TOTAL TAB/CAP	$5,715.4	100.0%	8.9%	221.5	100.0%	0.1%

U.S. Market Projections

Resistance to antibiotics is likely to increase, creating opportunities for new agents with activity against resistance. Physicians will be urged to choose agents with an appropriate spectrum of activity relative to the infection being treated. Resistance will increasingly become part of the promotional mix for emerging agents. The ability of an agent to treat resistant strains and the real or perceived ability to slow or prevent resistance development (mutation prevention concentration, low mutation frequency, structure-activity relationships, etc) may confer competitive advantage to such agents.

- Quinolones, which historically have seen limited use in community-acquired respiratory infections, will become a significant class in this segment as new agents from this class are launched that specifically target RTIs.

- The market will become more competitive as new agents enter both the community segment (ketolides, quinolones) as well as the nosocomial segment (oxazolidinones, streptogramins, everninomycins, peptides, others).

- Several key branded antibiotics will lose patent exclusivity over the next three to five years.. This may create an opportunity in the pediatric market as the top three pediatric brands (Augmentin, Cefzil, Zithromax) are among those losing patent exclusivity.

Antiviral influenza and cold therapeutics, as well as an increasing number of antibacterial vaccines may have a negative impact on antibiotic prescriptions.

The Ex-U.S. Market

Ex-U.S. sales of antibiotics totaled $11.7 billion in 1999. Tab/cap represents the largest segment, with sales of $9.4 billion from 770 million total prescriptions. Total Rx growth has been flat, with a 1996-99 CAGR of 0.5%. The use of antibiotics is predicted to slowly decline due to more judicious use of antibacterials in the face of increasing bacterial resistance.

Ex-U.S., the quinolone class accounted for 8% of total tab/cap market prescriptions (62 million Rxs) and 13% of sales ($1.2 billion). Ciprofloxacin is the market leader ex-U.S. with approximately 47% of the quinolone market Rxs (29 million Rxs) and 44% ($530MM) of sales. Levofloxacin launched in many European markets in 1998/1999 and holds approximately 14% Rx share of the European quinolone market and 0.8% of the overall tab/cap market. Although grepafloxacin and trovafloxacin also launched in some European countries in 1999, both products were recently pulled from the market due to liver toxicity and other complications. Moxifloxacin launched in Germany in Q4 1999, but has not yet been approved in other markets. In Japan, levofloxacin launched in 1994 and still commands a 65% Rx share of the quinolone market and 10% of the Japanese tab/cap market overall. Japan accounts for approximately 80% of ex-U.S. levofloxacin sales ($370MM).

CONFIDENTIAL
JH 008155

Scientific Rationale for ABT-773

The likely profile of ABT-773 justifies further development:

- ABT-773 pertains to a new class of antibiotics.
- Good activity against resistant Gram + organisms, particularly macrolide-resistant *S. pneumoniae*.
- Convenience, safety, and tolerability profile competitive with Z-pak.
- Oral Suspension and I.V. forms enabling penetration into pediatrics and hospital segments.

Clinical Studies

The safety and efficacy of ABT-773 in AECB were studied in a multi-center Phase II clinical trial conducted between January and April of 1999. Dosing regimens of 100mg TID and 200mg TID were tested. Of the 169 enrolled patients, 159 were clinically evaluable and 96 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 100mg TID	ABT-773 200mg TID	Overall Eradication
S. pneumoniae	100% (13/13)	90% (9/10)	96% (22/23)
M. catarrhalis	100% (6/6)	100% (7/7)	100% (13/13)
H. influenzae	96% (23/24)	92% (24/26)	92% (47/50)
H. parainfluenzae	100% (6/6)	88% (7/8)	93% (13/14)

Clinical Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (77/80)	92% (73/79)
Failure	4% (3/80)	8% (6/79)

Clinical and Bacterial Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (46/48)	94% (45/48)
Failure	4% (2/48)	6% (3/48)

Adverse Events	ABT-773 100mg TID	ABT-773 200mg TID	Overall
Taste Perversion	5% (4/84)	8% (7/85)	6.5% (11/169)
Diarrhea	11% (9/84)	6% (5/85)	8% (14/169)
Nausea	2% (2/84)	2% (2/85)	2% (4/169)
Abdominal Pain	1% (1/84)	2% (2/85)	2% (3/169)
Headache	2% (2/84)	1% (1/85)	2% (3/169)
Rash	2% (2/84)	1% (1/85)	2% (3/169)
Dyspnea	2% (2/84)		1% (2/169)
Elev. Liver Funct. Test	1% (1/84)	1% (1/85)	1% (2/169)
Fever		2% (2/85)	1% (2/169)

CONFIDENTIAL
JH 008156

The safety and efficacy of ABT-773 in AECB were studied in a multi-center Phase IIb clinical trial from October 1999 to March 2000. Doses of 150mg QD, 300mg QD, and 600mg QD were tested. Of the enrolled subjects, 342 were clinically evaluable, and 169 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 150mg QD		ABT-773 300mg QD		ABT-773 600mg QD		Overall Eradication	
S.pneumoniae	83%	(10/12)	90%	(9/10)	100%	(13/13)	91%	(32/35)
M.catarrhalis	80%	(8/10)	92%	(12/13)	91%	(10/11)	88%	(30/34)
H. influenzae	94%	(17/16)	89%	(17/19)	83%	(19/23)	88%	(53/60)
Clinical Response								
Cure	87%	(98/113)	90%	(105/117)	90%	(101/112)		
Failure	13%	(15/113)	10%	(12/117)	10%	(11/112)		
Clinical & Bacteriological Response								
Cure	84%	(42/50)	88%	(49/56)	94%	(59/63)		
Failure	16%	(8/50)	12%	(7/56)	6%	(4/63)		
Adverse Events								
Taste Perversion	5%	(4/84)	19%	(25/129)	29%	(37/129)	17%	(66/384)
Diarrhea	13%	(16/126)	12%	(15/129)	21%	(27/129)	15%	(58/384)
Nausea	7%	(9/126)	13%	(17/129)	30%	(38/129)	17%	(64/384)
Vomiting	2%	(3/126)	3%	(4/1229)	11%	(14/129)	5%	(21/384)
Nausea & Vomiting	0	(0/126)	<1%	(1/129)	4%	(5/129)	2%	(6/384)
Abdominal Pain	4%	(5/126)	4%	(5/129)	4%	(5/129)	4%	(15/384)

The safety and efficacy of ABT-773 in Acute Bacterial Sinusitis (ABS) were studied in a multi-center Phase IIb clinical trial conducted from October 1999 to March 2000. Dosing regimens of 150mg QD, 300mg QD, and 600mg QD were tested. Of the 292 enrolled subjects, 246 were clinically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 150mg QD		AB T-773 300mg QD		ABT-773 600mg QD		Overall Eradication	
S.pneumonia	3/3		8/8		9/12		20/23	
M. catarrhalis	8/9		3/4		4/4		15/17	
H. influenzae	3/5		7/7		5/7		15/19	
S.aureus	1/1		1/1		3/4		5/6	
Clinical Response								
Cure	89%	(70/79)	83%	(70/84)	71%	(59/83)		
Failure	11%	(9/79)	17%	(14/84)	29%	(24/83)		
Adverse Events								
Taste Perversion	1%	16/97)	14%	(14/98)	27%	(26/97)	14%	(41/292)
Diarrhea	6%	(6/97)	6%	(6/98)	17%	(16/97)	10%	(28/292)
Nausea	3%	(3/97)	12%	(12/98)	26%	(25/97)	14%	(40/292)
Vomiting	1%	(1/97)	6%	(6/98)	17%	(16/97)	8%	(23/292)

CONFIDENTIAL
JH 008157

The safety and efficacy of ABT-773 in community-acquired pneumonia (CAP) were studied in a multi-center Phase IIb clinical trial from October 1999 to March 2000. Dosing regimens of 300mg QD and 600mg QD were tested. Of the 187 enrolled subjects, 1248 were clinically evaluable, and 15 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Bacterial Eradication	**ABT-773 300mg QD**		**ABT-773 600mg QD**		**Overall Eradication**	
S. pneumoniae	87%	(13/15)	100%	(7/7)	91%	(20/22)
M. catarrhalis	75%	(6/8)	50%	(2/4)	67%	(8/12)
H. influenzae	100%	(9/9)	72%	(13/18)	81%	(22/27)
M. pneumoniae	93%	(13/14)	93%	(14/15)	93%	(27/29)
C. pneumoniae	95%	(19/20)	79%	(19/24)	86%	(38/144)
L. pneumoniae	100%	(3/3)	100%	(2/2)	100%	(5/5)
Clinical Response						
Cure	92%	(72/78)	80%	(56/70)		
Failure	8%	(6/78)	20%	(14/70)		
Clinical & Bacterial Response						
Cure	92%	(54/59)	82%	(47/57)		
Failure	8%	(5/59)	18%	(10/57)		
Adverse Events						
Taste Perversion	17%	(16/95)	26%	(24/92)	21%	(40/187)
Diarrhea	14%	(13/95)	19%	(17/92)	16%	(30/187)
Nausea	12%	(11/95)	22%	(20/92)	17%	(31/187)
V omitting	10%	(9/95)	15%	(14/92)	12%	(23/187)

- Appendix 1

Key Emerging Competitors

Generic	Brand	Company	Class	Status
moxifloxacin	Avelox	Bayer	Quinolone	Approved by FDA 12/13/00
gatifloxacin	Tequin	BMS	Quinolone	Approved by FDA 12/21/00
gemifloxacin	Factive	SKB	Quinolone	Filed NDA 12/15
T-3811	TBD	BMS/Toyama	Quinolone	Phase I
telithromycin	Ketek	Aventis	Ketolide	Filed NDA 3/00
linezolid	Zyvox	Pharmacia	Oxazolidinone	Approved by FDA Q2 '00

CONFIDENTIAL
JH 008158

CONFIDENTIAL

ABT – 627

Descriptive Memorandum

February 2001

Abbott Laboratories

ABT-627

Opportunity Overview

ABT-627 is an orally bioavailable endothelin antagonist with a high selectivity for the Eta receptor. The endothelins (ET-1, ET-2, ET-3) are a family of 21 amino acid peptides first identified in 1988. Endothelin is a potent, long acting vasoconstrictor produced by vascular endothelial cells. The known biological effect of ET-1 are believed to be mediated principally through the Eta receptor. These include potent and uniquely sustained vasoconstriction of vascular smooth muscle, positive inotropy of myocardium, and the stimulation of cell proliferation or the hypertrophy in vascular smooth muscle cells, cardiac myocytes, and fibroblasts.

In vitro studies in cultured cells have established that ABT-627 selectively binds to the Eta receptor, and that ABT-627 is a potent inhibitor of ET-1 binding to the Eta receptor.

Studies in cultured human prostate cancer cells and other cultured cells have shown that ABT-627 acts as a functional antagonist of ET-1, and these effects have been confirmed in vivo by assessing the effect of ABT-627 on the ET-1 induced pressor response in rats. Further animal studies have suggested that oral ABT-627 may be effective in the treatment of congestive heart failure, pulmonary hypertension, hypertension, arterial restenosis, and myocardial infarction.

In addition to literature and animal models supporting the role of endothelin antagonists in cardiovascular indications, data exists supporting the role of the ET-1 cytokine as a pathogenic mediator in cancer.

The current role of endothelin in the manifestations of metastatic prostate cancer (PCA) and other tumors have yet to be fully defined. However, Abbott scientists and thought leaders have made multiple observations about endothelin biology which suggest that endothelin may play a role in the biology and pathophysiology of metastatic prostate disease and other metastatic disease such as ovarian, cervical and renal tumors

ABT-627 has successfully completed Phase II trials for PCA, and the results demonstrate efficacy in hormone refractory PCA. The end of Phase II meeting with the FDA was held on October 4th. The data from Phase II was very favorably received and "best package" comments were made. Fast track designation and rolling NDA were granted. The FDA was conceptually in agreement with preliminary design of Phase III clinicals and clinical end points to measure. While not a dictate, a second Phase III trial will likely be conducted to insure the best opportunity for a successful outcome. The Phase III program is scheduled to commence before year-end. It is expected that filing on ABT 627 will occur in US and ex-US 1Q 2004. The compound is also in Phase I trials for other cancer types. Phase II studies in other cancer types will commence in 2Q01. Other indications outside of oncology are also being considered, to optimize the commercial potential of this asset.

CONFIDENTIAL
JH 008160

The US Market

Prostate cancer is the most common cancer to strike nonsmoking men. The NCI estimates that there are over 1.7 million men living with prostate cancer in the U.S., and another 179,300 will be diagnosed in 1999. Nearly 80% of these cases are men over 60 years of age. It is estimated that the prevalence of prostate cancer is 380,000 in Western Europe and 45,000 in Japan. While the vast majority of these patients will be identified with potentially curable disease (25% in Stage I and 50% in Stage II) in the U.S., half of these patients will go undiagnosed until late stage disease in W. Europe and Japan. The skewed distribution of diagnosed cases ex-U.S. is largely due to less aggressive prostate cancer screening programs compared to the U.S.

Prostate cancer has seen few additions or innovations in treatment regimens in the past two decades. Treatments remain, in general, radical prostatectomy (RP) for localized disease, radiotherapy for locally advanced disease and hormone therapy for advanced disease. Patients receiving hormone therapy become refractory to this treatment after two to three years, although many will continue on hormone therapy. These hormone refractory prostate cancer (HRPCa) patients usually have a life expectancy of approximately 12 months, and no existing standard of care exists for treating these patients. No therapy has shown a significant impact on survival in these patients, although some chemotherapeutic regimens may offer promise.

There is a general trend toward using hormone therapy in earlier stage patients. In some centers, patients are receiving hormone therapy prior to surgery or radiation, in an attempt to improve outcomes in these definitive treatments. Some thought leaders suggest that this earlier utilization has contributed to the overall mortality improvements in PCA. Studies are ongoing looking at different uses for hormone therapy, including intermittent therapy, in an attempt to improve outcomes and mitigate the morbidity associated with hormonal therapy.

Hormone therapy remains the mainstay of prostate cancer treatment in earlier stages. Chemotherapy, however, has gained additional attention in hormone refractory disease as new combinations and regimens offer the potential for greater therapeutic benefit with fewer side-effects. This trend will take several years before clinical trials are completed and community based oncologists adopt these regimens, so the current cytotoxic market in PCA is small.

The total dollar growth of this market has slowed as the two market leaders, Lupron (leuprolide/TAP) and Zoladex (goserelin/Zeneca), have experienced increased price pressures from managed care and Medicare. About half the states are currently reimbursing these therapies at a least cost option (only paying for the cheapest alternative), putting downward price pressures on Lupron ($6,500/yr) to match Zoladex's ($4,500/yr) lower price point. Thus, US Lupron dollar sales declined between 1997 and 1998, despite an increase in patient volume.

Growth has also stagnated due to a lack of innovation in this hormone dominated category. There have been few therapeutic advances in the treatment of PCA in the last 5 years.

The only chemotherapy approved for use in HRPCa patients with pain is Novantrone (mitoxantrone/Immunex), but the marginal benefits this compound delivers is deeply undercut by its severe toxicities and a lifetime cap on dose. Novantrone and steroids significantly reduced the metastatic pain in 40% of patients, but it does not appear to provide a survival advantage. Novantrone is dosed by i.v. infusion every 21 days, at a cost of $560 per treatment, or an annual cost of around $8,000. Use of this agent is associated with significant side-effects, including myelosuppression, cardiac toxicity (which limits dosing) and nausea. It is this negative side-effect profile that inhibits the use of this agent in more patients. Only about 4% of U.S. HRPCa patients received Novantrone therapy in 1998. Novantrone has not been approved ex-US.

Only about 17% of HRPCa patients received any chemotherapy in 1998. The most common drugs included estramustine, paclitaxel and etoposide. These drugs continue to be some of the most studied compounds in HRPCa ongoing research and represent the greatest short-term promise in the cytotoxic treatment of this advanced disease state.

CONFIDENTIAL
JH 008161

US Sales of Products to Treat Prostate Cancer

Product	1997 Dollar Sales (MM)	1998 Dollar Sales (MM)	% chng '97-'98
Lupron (leuprolide/TAP)	$650	$667	2.6%
Zoladex (goserelin/Zeneca)	233	296	27.3
Casodex (bicalutamide/Zeneca)	58	68	17.24
Eulixen (flutamide/Schering)	74	67	-9.5
Novantrone (mitoxantrone/Immunex)	33	35	6.1
Nilandrone (nilutamide/Hoechst)	12	24	100
Emcyt (estramustine/Pharmacia/Upjohn)	8	14	75
Taxol (paclitaxel/BMS)	4	8	100
VePesid (etoposide/BMS)	5	4	-20
Others	27	31	14.8
Total	1,104	1,214	10%

Source: Tandem Research and Price Probe

US Market Projections

- Novantrone (mitoxantrone/Immunex) is currently the only product approved for the treatment of hormone refractory PCA with pain. It currently falls short on the market needs in terms of efficacy and side-effect profile.

Attribute	Novantrone Profile
Dosing	I.V. infusion cycles
Cost	Expensive, ~$10,000/yr
Efficacy	Provides marginal improvements in quality of life
Reimbursed	Yes
Side-effects	Dose limiting toxicities
Promo Efforts	108 oncology reps
Targets	Oncologists

Several surveys indicate that there are over 100 compounds in preclinical and clinical development for prostate cancer and various solid tumors. The compounds listed in the appendix represent compounds that appear to offer the greatest promise and/or potential for competition for ABT-627. However, since the most likely use of ABT-627 will be in combination with best therapy, it is difficult to define the extent of competitive threat that any of these compounds represent. In general, other cytostatic agents probably offer the greatest threat as a replacement for ABT-627. However, even other cytostatic agents may be combined to maximize the activity of the various mechanisms.

To date, PPD is aware of only one other endothelin receptor antagonist in development for cancer, from Yamanouchi, which began Phase I studies in the Fall of 1999. ABT-627 is still poised to be the first endothelin receptor antagonist to reach the market for oncology.

Scientific Rationale for ABT-627

There are relatively low hurdles for entry for a product to treat hormone refractory prostate cancer, as no truly effective agents presently exists. Quality of life is paramount in this population, followed by improvements in disease progression and survival. Quality of life parameters could include an impact on pain/or delay in pain onset or other performance type measures of daily activities. As all hormone therapy ultimately fails, a product that delays disease progression is needed.

Unmet Need	Pipeline Impact
Improvements in QOL	• ABT-627's profile goal is to provide improvements to a patient's QOL or blunt a decrease in QOL • Cytotoxic agents rarely have significant positive impacts on QOL • Other cytostatic agents may offer this benefit
Improvements in survival	• It is unlikely that improvements in survival will be seen in our current trials • Cytotoxic agents may offer a survival advantage, perhaps in combination with ABT-627
Improvements in time to disease progression	• Cytostatic and cytotoxic agents offer the greatest promise for this benefit

Our objective is to provide physicians and patients with a novel option for the treatment of hormone refractory prostate cancer, distinguish ABT-627 from current cytotoxic therapies and encourage the treatment of advanced prostate cancer patients currently only receiving hormonal therapy.

ABT-627 will be positioned as a physician and patient-friendly choice for advanced prostate cancer patients who have failed hormone therapy. ABT-627's novel mechanism of action provides a delay in disease progression and a positive impact on QOL. The oral, QD dosing enhances compliance and minimizes disruptions to daily living.

The message will focus on 3 key attributes:

- Efficacy (defined as increased time to tumor progression) in a patient group with few options
- Improvements in quality of life
- Convenience

Physicians no longer have to choose between *treating* advanced prostate cancer patients and a patient's quality of life. ABT-627 has a positive impact on disease progression and symptoms associated with quality of life, without the baggage of significant side-effects or the inconvenience of parenteral administration associated with current therapy choices.

This message expresses the key features of the agent in terms of patient benefits, as opposed to emphasizing the scientific/clinical aspects. Since prostate cancer is a terminal disease with a relatively long time for disease progression, the quality of a patient's life becomes even more critical. Especially in cancer treatment, where the therapy can often feel worse than the disease, the benefits that ABT-627 will bring, coupled with its benign side-effect profile, will have a significant impact on prostate cancer patients' lives.

Clinical Studies

Phase II trials have been completed and the data are being analyzed. Preliminary results for the primary endpoint of time-to-disease progression and the secondary endpoint of time-to-PSA progression show that ABT-627 favorably delays both phenomena with a benign adverse event profile. The results are summarized below:

Disease Progression: The delay in median time-to-disease progression for evaluable subjects was improved by 52% and 43% for the 10mg and 2.5mg doses respectively over the placebo time-to-disease progression of 4.3 months.

Time-to-PSA Increase: A 150% and 150% improvement in median time-to-PSA progression for evaluable subjects was observed for the 10mg and 2.5mg doses respectively over the time-to-PSA progression placebo of 2 months.

Significant dose related decreases were observed in markers of metastatic bone disease.

Key Prostate Cancer Competitors

Product	Company	Phase	Projected NDA Filing	Description	Anticipated impact on ABT-627
AG 3340	Agouron	III	2000	MMPI	In combination with mitoxantrone/prednisone. Unknown impact.
Marimastat	British Biotech	II	2001	MMPI	Side-effect profile significantly worse than ABT-627. Probably minimal impact.
SU 101	Sugen	I/II	2002	PDGF TK antagonist	Phase III in combination with mitoxantrone set to start in 1999. Uncertain impact.
AR 623	Aronex	II	2002	All-transretinoic acid	IV liposomal form of ATRA. HRPCa trial began November 1998. Probably additive.
MGI 114	MGI Pharma	II	2002	Alkylating agent	Lead compound in acylfulvenes. Fairly toxic. Probably additive.
Liposomal Encapsulated doxorubicin	NeoPharm and P&U/Alza and others	II	2002	Anthracycline	Various forms being developed by various companies. Probably additive.
Sataraplatin	BMS	III	2000	Platinum complex	Oral platinum analog w/toxicities comparable to carboplatin. Probably additive.
Taxol	BMS	II	2001	taxane	In various combinations with other chemo agents. Probably additive.
Taxotere	RPR	II	2001	taxane	In various combinations with other chemo agents. Probably additive.

CONFIDENTIAL
JH 008164

CONFIDENTIAL

ABT-594

Descriptive Memorandum

February 2001

Abbott Laboratories

ABT-594 Opportunity Overview

ABT-594 is a non-opioid, non-NSAID analgesic that is a potent and selective neuronal nicotinic receptor (NNR) agonist being studied for the treatment of pain. ABT-594 is 30 to 100-fold more potent and equally efficacious to morphine in several well-characterized animal models of pain. The preclinical side effect and dependency liability profile of ABT-594 is superior to that of morphine.

ABT-594 is orally administered, and BID dosing is expected. Its initial targeted indication is symptomatic treatment of diabetic neuropathic pain. It is covered by a composition of matter patent through June of 2016, and also has a use patent pending in analgesia that would provide protection through September of 2017.

The IND filing of ABT-594 was in December 1998. A Phase IIb (dose ranging) trial began April 2000 in diabetic neuropathic pain. A Go/No Go decision for clinical efficacy is expected June 2001. The NDA filing is expected in 3Q2003. Development of additional formulations is under consideration (parenteral, transdermal, extended-release).

U.S. sales in 1999 for the key neuropathic pain treatments, Neurontin, carbamazepine, and tricyclic antidepressants (TCAs), are estimated to be $350 million. Neurontin sales account for the bulk of this, with an estimated 40% of this antiepileptic drug's sales being for neuropathic pain. Neurontin's 2000 sales are expected to reach $1 billion with perhaps 50% of its use in neuropathic pain. This dollar market value likely underestimates this market's potential due to a number of factors. Only the anticonvulsant, Tegretol (carbamazepine), currently off patent, and Lidoderm, a lidocaine patch, have specific indications for a type of neuropathic pain (trigeminal neuralgia and post-herpetic neuralgia, respectively) in the U.S. Currently, there is an unmet market need for novel neuropathic pain treatments such as ABT-594. Therefore, this compound is likely to be well received in this arena. Outside the U.S., Neurontin recently received an indication in the U.K. for the treatment of neuropathic pain. Despite these opportunities, there has been little to no funding from the pharmaceutical industry to improve diagnosis and treatment of neuropathic pain and drive market growth.

Ex-U.S. sales of carbamazepine and Neurontin for treatment of neuropathic pain are estimated to be approximately $140MM in 1999. Carbamazepine is still the treatment of choice ex-U.S., with estimated sales of approximately $90MM in neuropathic pain. Neurontin has achieved only $53MM in sales for this pain segment, with a price approximately 3-4 times that of carbamazepine, suggesting a patient share of only 10-20%.

Nociceptive pain is categorized by duration (acute or chronic) and by severity (mild, moderate, and severe). The mild and, to a lesser extent, moderate segments have multiple product entries and are generally well satisfied by OTC products such as aspirin, acetaminophen and ibuprofen. The prescription market for nociceptive pain is made up of four key classes of analgesics: NSAIDs, COX-2s, Opioids (and combination products), and Other Non-Opioids. In 1999, sales for these four classes of analgesics exceeded $12BB ($6.7BB U.S., $5.6BB Ex-U.S.)

CONFIDENTIAL
JH 008166

Market Size / Prevalence

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. Chronic pain, including both neuropathic and nociceptive pain, is considered to be the single most common cause of suffering and disability in the industrialized world with an estimated 25-30% of the population experiencing some form of chronic pain.

Neuropathic pain is a frequent sequela of diabetes, cancer, AIDS and other viral infections, as well as entrapment neuropathies such as carpal tunnel syndrome. Diabetes and its associated complications are increasing at an alarming rate in the United States. Despite advances in treatment, the development of diabetic complications such as neuropathy remains significant. The diagnosed prevalence of diabetic neuropathy is estimated to be about 2 to 3 million patients, with at least 10 to 20% of those patients experiencing painful symptoms (~200,000 to 600,000.) AIDS-related neuropathic pain is estimated to affect approximately 40% of HIV-infected individuals (~14 million.) Post-herpetic neuralgia (PHN) is another virally induced neuropathic pain syndrome. Annually, acute herpes zoster infection (shingles) occurs in almost a quarter of a million people over the age of 60 in the U.S. alone. Pain lasting more than one year has been reported in 22% of patients over the age of 55 and in 48% of those over 70 years of age. In cancer, nerves can be damaged by mechanical distortion from a tumor mass, infiltration by tumor, chemotherapy, or radiation therapy and, therefore, neuropathic pain is common. An estimate of the prevalence rate for cancer-related neuropathic pain in the U.S. is 200,000 people.

Chronic nociceptive pain categories include osteoarthritis (OA), chronic back and neck pain, rheumatoid arthritis (RA), and cancer pain. These diagnoses are expected to become more prevalent as the population ages. Current overall prevalence for these disorders is staggering (over 200 million worldwide) and, although the diagnosed and treated populations are lower, improved treatment options and awareness have the potential to drive significant growth. OA is one of the most common nociceptive pain conditions treated by primary care physicians and three-fourths of OA sufferers surveyed indicate that the disease interferes with their daily activities. Chronic back and neck pain are also highly prevalent and represent an estimated 40% of a primary care physician's (PCP's) chronic pain patient population.

CONFIDENTIAL
JH 008167

Competition, Current Marketed Products:

The following tables show the factored U.S. and ex-U.S. prescription and sales volume for key neuropathic pain therapies in 1999.

1999 Key Neuropathic Pain Products, Estimated TRxs

Product/Class	1999 U.S. TRx (MM)	U.S. TRx CAGR '97-'99	1999 ex-U.S. TRx (MM)	ex-U.S. TRx CAGR '97-'99
Neurontin	3.3	26.3%	N/A	N/A
carbamazepine	1.0	12.6%	N/A	N/A
TCAs	8.2	1.1%	N/A	N/A
TOTAL	12.5	5.6%	N/A	N/A

Source: IMS, factored for neuropathic uses.

N/A = not available

1999 Key Neuropathic Pain Products, Estimated $ Sales

Product/Class	1999 U.S. Sales ($MM)	U.S. Sales CAGR '97-'99	1999 ex-U.S. Sales ($MM)	ex-U.S. Sales CAGR '97-'99
Neurontin	$308	28.7%	$53	57.6%
carbamazepine	$17	13.1%	$87	2.5%
TCAs	$26	-3.3%	N/A	N/A
TOTAL	$351	21.7%	$140	10.1%

Source: IMS, factored for neuropathic uses; Ex-U.S. data includes retail pharmacy data from all audited markets

N/A = not available

Competition, Products in Development

Almost 100 compounds are currently in development for prescription pain management, though some of these compounds are also being developed for non-analgesic indications. Most of the analgesic compounds in the pipeline represent incremental improvements over the opioids or NSAIDs, or consist of new formulations or delivery mechanisms for the standard analgesics. Fewer than 30% of the compounds in development have novel mechanisms of action. Drugs with novel mechanisms are expected to provide the bulk of promoted competition for ABT-594.

In addition to the novel analgesics in the table below, a number of new formulation and combination products, most often containing an opioid, are in development. Second generation COX-2s are also in development but are not likely to represent major breakthroughs on the scale of the first generation products.

CONFIDENTIAL
JH 008168

Analgesia Development Pipeline – Key Novel Agents				
Product	**Company**	**Mechanism**	**Phase**	**Comments**
pregabalin	Pfizer	Unknown; possibly through (2™ subunit binding	III	Neuropathic pain; chronic pain, follow-up to Neurontin
saredutant	Sanofi	NK-2 receptor antagonist	II	General pain; MOA losing favor; active program
ZD4952, ZD 6416	Zeneca	Prostaglandin receptor antagonist	II	Moderate to severe pain, neurogenic pain
GV196771	Glaxo	Glycine antagonist	II	Chronic pain; showing promise
Tepoxalin	Johnson & Johnson	COX/5-LO inhibitor	II	OA, described as 'steroid replacing anti-inflammatory drug'
darbufelone	Parke-Davis	COX/5-LO inhibitor	II	General pain
117mSn DTPA	Brookhaven National Lab/Diatide	Unknown	II	Cancer pain Bone cancer (preclinical)
cizolirtine	Esteve	Substance P agonist	II	Analgesia, antipyretic
ADD 234037/ harkoseride	Houston University	Glycine NMDA associated antagonist	II	Neurogenic pain
LY303870/ lanepitant	Eli Lilly	Neurokinin 1 antagonist	II	Pain (migraine – discontinued)
colykade devacade	Merck	Cholecystokinin B antagonists	II	Pain (UK)
RPR 100893 dapitant	Aventis	Neurokinin 1 antagonist	II	Pain (France)
prosaptide TX14A	Myelos Neurosciences	Unknown	I/II	Diabetic neuropathies, Pain
CNS 5161	Cambridge NeuroScience	Glutamate antagonist, NMDA receptor antagonist	I	Neurogenic pain
HCT-3012	NicOx	Nitric oxide NSAID	I	Pain and inflammation
Sources: ADIS, IMS, Decision Resources, company reports				

CONFIDENTIAL
JH 008169

Analgesia Development Pipeline – Nicotinic Mechanisms			
Product	**Company**	**Phase**	**Comments**
GTS-21	Taisho	II	Target is Alzheimer's disease; may have preclinical pain program; looking for partner
CMI 980	Cytomed	Preclinical	Target is pain; epibatidine analog
SIB-T1887	Sibia	Preclinical	Target is pain
FID 072021	Fidia	Preclinical	Target is pain; not actively funding
Sources: ADIS, IMS, company reports			

Unmet Needs

In general, a significant unmet need exists for safer, non-abusable, non-addicting, non-tolerance-producing, and non-scheduled efficacious oral and parenteral analgesic products for the treatment of moderate to severe neuropathic and chronic nociceptive pain.

Unmet Market Needs and the Impact of the Pipeline	
Unmet Need	**Pipeline Impact**
Efficacy in moderate to severe pain without tolerance, dependence or abuse potential	Novel nicotinic agents like ABT-594 may provide efficacy in more severe pain states without opioid-like liabilities.
Efficacy in neuropathic pain	Pregabalin may provide incremental improvement in neuropathic pain efficacy over gabapentin, but may also have increased frequency of adverse events. Novel nicotinic agents like ABT-594 appear to have efficacy in neuropathic pain, based on animal models.
Reduction in the GI bleeding risk of NSAIDs	COX-2 inhibitors appear to reduce the incidence and severity of GI ulcers and bleeding; second generation COX-2s may increase therapeutic window further; ABT-594 may need to demonstrate low G.I. complication rate.
Overcome ceiling effect of NSAIDs	Preclinical studies did not indicate a ceiling effect for novel nicotinic agents like ABT-594.
Extended dosage intervals or novel delivery mechanisms for improved compliance and convenience	Once weekly dosing formulations being explored for COX-2s, etc. Transdermal patch technology improvements likely; may need to provide line-extension / alternate formulations for ABT-594.
Therapies aimed at disease modification, prevention	Agents that decrease rate of diabetic complications (e.g., aldose reductase inhibitors) or directly treat neuropathy (bimoclomol) may decrease incidence of neuropathic pain; thereby decreasing available market for ABT-594.

CONFIDENTIAL
JH 008170

Product / Development Background

Scientific Rationale for ABT-594

Recent findings in the understanding of pain mechanisms have led to new conceptual approaches to clinical pain and a new understanding of potential novel molecular targets for analgesic drug development. Molecular targets have included modulators of glutamate neurotransmission (NMDA antagonists), ion channel modulators (neuron specific calcium channels, TTX-resistant sodium channels), neurokinin antagonists (NK-1), and novel anti-epileptics targeting the calcium receptor. None of these approaches has yet produced compounds exhibiting broad-spectrum analgesic efficacy with decreased side effect liability.

ABT-594 is a non-opioid, non-NSAID analgesic that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of pain. The preclinical side effect and dependence liability profile of ABT-594 is superior to that of morphine. Mechanistically, ABT-594 is a potent and selective neuronal nicotinic receptor (NNR) agonist with high oral bioavailability in rat, dog, and monkey.

In pre-clinical studies, ABT-594 rapidly distributes to the brain following systemic administration and, like morphine, can work at multiple levels in the central and peripheral nervous system to modulate pain perception. ABT-594 produces antinociceptive effects by interacting at both central and peripheral nAChRs. Injections of ABT-594 into brain at doses 1000-fold lower than given peripherally produce marked antinociceptive activity, indicating that ABT-594 can also activate descending pathways from the CNS to modulate pain processing. It also inhibits the release of the primary nociceptive transmitters, substance P and calcitonin gene related peptide (CGRP) *in vitro*, at the level of the dorsal horn of the spinal cord suggesting that ABT-594 can attenuate mechanisms leading to neurogenic inflammation, central sensitization and consolidation of pain-mediated neuronal changes.

ABT-594 is expected to be a highly differentiated product. It is expected to be the first neuronal nicotinic receptor agonist to receive an indication for pain. It has a novel mechanism of action and a potentially broad coverage of chronic pain conditions. In addition, it has an opioid-like efficacy without tolerance, dependence or abuse potential, while having equivalent/superior efficacy to other drugs used to treat neuropathic pain.

Clinical Studies

Human clinical trials began in 1997. Phase I trials with an oral solution formulation indicated that 150ug/day would be the maximum tolerated dose. Results from subsequent phase I and phase II trials with soft elastic capsule (SEC) and hard gelatin capsule (HGC) suggest that higher doses would be tolerated. Phase IIa studies with ABT-594 SEC formulation suggest a trend towards analgesic effect at 75ug BID, the maximum dose studied in this protocol. ABT-594 was generally well tolerated in these studies. The most common adverse events for subjects receiving ABT-594 75ug BID were nausea (15%), headache (13%), dizziness (7%), insomnia (6%), and vomiting (5%).

A phase IIb study for neuropathic pain at higher, titrated doses of ABT-594 began in April 2000 and ends in June 2001. A total of 320 patients is anticipated to be included in the study.

CONFIDENTIAL
JH 008171

Considerations

Target Profile:

The current status of ABT-594's profile vs. target profile is summarized in the table below:

Target Profile Attribute	**Probability**
Not scheduled (DEA)	High
Very few abnormal Liver Function Tests	High
Few Drug interactions	High
BID / TID dosing	High
No reduced efficacy or increased AEs in nicotine users	High
Onset of action 1.5 – 2.0 hours	High
Neuropathic efficacy	Medium
No tolerance, dependence or withdrawal	Medium
Other safety OK	Medium
No cravings in ex-nicotine users	Medium
Low nausea / vomiting	Low

Label Strategy:

BASE: Indicated for the treatment of diabetic neuropathic pain.

UPSIDE:
1) Treatment of pain associated with OA
2) Treatment of post-herpetic neuralgia
3) Treatment of neuropathic pain
4) Treatment of chronic pain
5) Treatment of cancer pain

Cost of Goods Sold:

The projected average daily dose is expected to be a maximum of approximately 600 mcg base equivalent / day. Based upon this dosage projection and the estimated cost of bulk drug substance of $40M per Kg base equivalent, the estimated cost for drug substance at launch will be approximately $0.024 per day.

CONFIDENTIAL
JH 008172

Pricing:

US: Pricing new, and particularly novel, products at a reasonable premium will likely continue to be the norm in the years leading up to the launch of ABT-594. Current forecast assumptions put the price of ABT-594 at a level comparable to Celebrex and Neurontin, grown at a modest 2% per year to launch year AWP of approximately $95 for a 30 day prescription.

Ex-US: New pain medications must demonstrate a true advantage in efficacy and/or side effects to receive regulatory approval, especially by the European Medicines Evaluation Agency (EMEA); assuming the target efficacy and tolerability profile of ABT-594 is achieved, ABT-594 would meet this requirement. Because ABT-594 may have application in both neuropathic and chronic nociceptive pain, the ex-U.S. pricing assumption for ABT-594 is comparable to COX-2 pricing. The current average price for COX-2's is approximately $1.10 per day; however, this reflects a large percentage of sales in "free-pricing" countries, where COX-2s launched first, which tend to have higher than average prices. Therefore, the average ex-U.S. price for ABT-594 is assumed to be $0.90/day.

CONFIDENTIAL
JH 008173

CONFIDENTIAL

ABT - 751

Descriptive Memorandum

February 2001

Abbott Laboratories

ABT-751

Opportunity Overview

Cytotoxic agents and hormones constitute the dominant classes of drugs available to treat cancer and are responsible for 96% of the total market. Since 1993, Taxol, a taxane developed and marketed by BMS, has been widely used. Another taxane, Taxotere, developed and marketed by Aventis, was launched in 1996. Combined worldwide sales of these two products were of nearly $2 Billion US in 1999. Clinically, the development of drug resistance is the primary factor that limits the efficacy achievable with these drugs.

Abbott's anti-mitotic agent (ABT-751) is a novel, oral cytotoxic agent that acts by a mechanism similar to that of the taxanes but retains activity against taxane resistant cells. ABT-751 binds to the colchicine site on tubulin and inhibits the *in vitro* polymerization of microtubules. The interference with normal microtubule dynamics leads to a block in the cell cycle at the G2/M phase that ultimately results in the induction of cellular apoptosis. ABT-751 is a potent antimitotic agent that inhibits the proliferation of a broad spectrum of human tumor derived cell lines including those that are paclitaxel and doxorubicin resistant due to the multidrug-resistant (MDR) phenotype or other genetic changes.

ABT-751 demonstrated impressive oral antitumor activity when evaluated in both synegeic and human xenograft tumor models. The antitumor response was independent of the MDR status of the model, consistent with the activity observed in cell cultures. In sharp contrast with other cytotoxic drugs, the maximum tolerated dosage of ABT-751, on a q.d. 1-5 schedule, could be administered for an extended period (q.d. 1-21 or q.d. 1-28) resulting in a dramatic enhancement of the antitumor activity. These results suggest that the colchicine site ligands, such as ABT-751, will exhibit a broad spectrum of activity that will be distinct from that of other classes of antimitotic drugs. Oral availability of the compound is high. Taxol and Taxotere, in contrast, have no oral bioavailability.

The most significant finding in toxicology studies was a change in systemic and pulmonary vascular resistance following intravenous infusion of ABT-751 to anesthetized dogs. These effects led to an inverse response in cardiac output. Similar changes were observed following infusion of a structurally unrelated colchicine-site ligand, and therefore most likely represent a class effect. Additional toxicology studies focusing on vascular pathology will be performed to further elucidate this finding.

ABT-751 was administered to patients with advanced cancer in Japan in a Phase I study. Toxicities seen after single doses and 5 days of q.d. dosing were nausea, vomiting, diarrhea, epigastric pain, ileus and peripheral neuropathy. Grade 2 toxicity was peripheral neuropathy and associated paresthesias. Pharmacokinetic analyses showed plasma concentrations equivalent to those that affected systemic resistance and cardiac output in the anesthetized dog study. However, no adverse cardiovascular effects were observed in the Japanese Phase I trial. Evidence of ABT-751 efficacy was exhibited in one patient with uterine sarcoma, one patient with NSCLC after single doses, one patient with gastric cancer and one patient with uterine cervical carcinoma demonstrated decreased tumor markers after repeated dosing.

CONFIDENTIAL
JH 008175

The planned initial Phase I study in the U.S. will determine the maximum tolerated dose and dose-limiting toxicities of ABT-751 given orally once a day or twice daily for multiple cycles in patients with advanced malignancies. In addition, pharmacokinetics in a western population, and optimal dose and schedule will be determined. Phase II studies will be initiated in patients with different cancer types:

- •Refractory breast (taxane failures)
- •Hormone refractory prostate
- •Bladder
- •Lung
- •Cervical
- •Hepatocellular
- •Other possibilities: colorectal, sarcoma, renal cell, pancreatic, HNSCC

Cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market

Global Sales by Market Segment ($ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
Hormone	4,414	4,784	4,884	5,000	5.2%
Cytotoxic	4,278	5,212	6,268	7,300	21.0%
Adjunctive	3,367	3,651	4,166	4,900	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

Sales by Region ($ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex- US	6,495	7,370	7,896	8,700	10.3%

Source: Datamonitor

This growth of the cytotoxic segment has been driven primarily by the introduction of new, more effective and expensive therapies such as Taxol (paclitaxel/BMS), Gemzar (gemcitabine/Lilly), Taxotere (docetaxel/RPR) and Hycamtin (topotecan/SB). Uptake of these newer agents, however, can be dependent on the cost sensitivity of the local market.

The clinical targets identified for this compound include late stage breast cancer, late stage NSCL cancer (on-label), with late stage ovarian and pancreatic cancer as additional cancer types where efficacy has been demonstrated, but not filed. This product may also be potentially efficacious in cancers such as gastric, colorectal, prostate, bladder, esophageal, hepatocellular (ex US), lymphoma, and leukemia. Targets will be refined as we know more about this compound's in-vivo activity.

CONFIDENTIAL
JH 008176

The following tables summarize the key competitive products by indication (US data only):

Late Stage Breast

Product	Share
Cyclophosphamide/Cytoxan/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	16.25
Paclitaxel/Taxol/BMS	16.11
Trastuzumab/Herceptin/Genetech	11.26

Late Stage NSCL

Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

Late Stage Ovarian

Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/Alza	9.14
Cisplatin/Platinol/BMS	7.58

Late Stage Pancreas

Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Efudex/ICN Pharma	21.0
Leucovorin/	10.7
Cisplatin/Platinol/BMS	4.72

Compounds in Development

ABT-751 induces a mitotic block by binding to the colchicine site on tubulin and thereby affecting tubulin polymerization. There are no currently available drugs which function by the mechanism described above. However, vinca alkaloids and taxanes fall into the broad category of anti-mitotics although they produce the anti-mitotic effect through different mechanisms. The following table summarizes anti-mitotic compounds in development.

CONFIDENTIAL
JH 008177

Company	Compound	Indication	Status of compound	Status of project
Colchicine-site ligands				
Oxigene	combretastatin-A4 phosphate	Tumor vasculature	Phase I	active
Tularik	T138607 (phosphate prodrug)	Cancer (unspecified)	Phase I	active
Tularik	T900607	Cancer (unspecified)	Preclinical	active
ICI/CRC	Amphethinile	Cancer (unspecified)	Phase I (abandoned 1988)	inactive
Welcome Research	1069C	Cancer (unspecified)	Phase I (abandoned 1996)	inactive
NIH	Trimethylcolchicinic acid	Various tumors	Phase I (1990, abandoned)	inactive
Parke-Davis	CI-980	ovarian, colorectal	Phase II (abandoned 2000)	inactive
Vinca alkaloid-site ligands				
BASF	LU103793 (dolastatin 15 analog)	Cancer (unspecified)	Phase II (abandoned)	active
Servier	Vinxaltine	Cancer (unspecified)	Phase I	unknown
NCI	dolastatin 10	Adv. Cancers	Phase I	unknown
Teikoku Hormone	TZT-1027 (dolastatin 10 analog)	Cancer (unspecified)	Phase I (Jpn)	unknown
Lilly	LY 355703 (cryptophycin 52)	Cancer (unspecified)	Preclinical	unknown
Takeda	Maitansine	Cancer (unspecified)	Preclinical	unknown
Microtubule stabilizing agents (non-taxanes)				
Soc. Biotech. Res/ Bristol-Myers Squibb	Epothilone	Cancer (unspecified)	Preclinical	active
Bristol-Myers Squibb	eleutherobin	Cancer (unspecified)	Preclinical	active
Pharmacia & Upjohn	sarcodictyins	Cancer (unspecified)	Preclinical	active
Takeda	GS-164	Cancer (unspecified)	Preclinical	active

The novelty of this mechanism offers the promise of differentiation that will diminish the threat from potential competitors. However, this novelty is balanced by the similarity to current mechanisms, such as taxanes and vinca alkaloids, which suggests the promise of clinical efficacy. With the opportunity to be first or second to market with an agent that binds to the colchicine site, the competitive situation seems modest.

CONFIDENTIAL
JH 008178

CONFIDENTIAL

ABT – 492

Descriptive Memorandum

February 2001

Abbott Laboratories

CONFIDENTIAL
JH 008179

Hancock_ABT 492

ABT 492

Overview

The commercial success of fluoroquinolones such as ciprofloxacin and levofloxacin, along with the desire to further improve the properties of these compounds (microbiological spectrum and safety, for example) has led to fierce competition to identify analogs with superior therapeutic properties. In addition, the development of resistance to present antibiotics will drive a continued need for new agents. Goals for a quinolone antibiotic include broad-spectrum indications equal to trovafloxacin, antibacterial activity comparable to trovafloxacin, tolerability comparable to levofloxacin, oral and intravenous formulations, once daily dosing, length of treatment equal to moxifloxacin, and an acceptable cost of goods. ABT-492, an in-licensed compound from the Wakunaga Pharmaceutical Co., is being developed for evaluation to meet these goals.

The *in vitro* antibacterial activity of ABT-492 was consistently more potent than trovafloxacin against most quinolone-susceptible pathogens, including species responsible for community and nosocomial respiratory tract infections, urinary tract infections, blood stream infections, skin and skin structure infections, and anaerobic infections. The compound has potent activity against multidrug-resistant *S. pneumoniae* (penicillin-, macrolide-, tetracycline-resistant) and retained activity against *S. pneumoniae* strains resistant to other quinolones including trovafloxacin. ABT-492 was also highly active against anaerobes and ciprofloxacin-susceptible *P. aeruginosa*. ABT-492 was as active as trovafloxacin against *C. trachomatis*, indicating good intracellular penetration. Thus, ABT-492 is likely to be a useful broad-spectrum antibacterial agent. The enhanced antibacterial activity of ABT-492 relative to ciprofloxacin, levofloxacin, and trovafloxacin is likely to be explained, in part, by it's potent interactions with bacterial topoisomerases. ABT-492's equivalent activity against both the DNA gyrase and the topoisomerase IV of pathogens, give ABT-492 a potential for decreased development of resistance.

The *in vitro* potency data suggests that ABT-492 has the potential to be therapeutically effective at doses comparable to trovafloxacin and superior to levofloxacin. In addition, ABT-492 was consistently more potent than trovafloxacin against MRSA and vancomycin-resistant enterococci. In both these cases, however, therapeutic utility remains to be assessed in the clinical setting.

S. pneumoniae was chosen as the dose-defining pathogen since it is the key pathogen in severe respiratory tract infections and treatment of infections caused by this pathogen has traditionally been a weakness of most quinolones. For treatment of fluoroquinolone-susceptible *S. pneumoniae* respiratory tract infections, oral dosing may be similar to trovafloxacin based on data generated in lung infection models. Because of the excellent potency of ABT-492 against fluoroquinolone-resistant *S. pneumoniae* with an MIC_{90} of 0.12 µg/ml, this group of emerging strains may be targeted as a key differentiation point from other quinolones. Also, data from the thigh infection model suggests significantly greater efficacy for ABT-492 than for trovafloxacin.

The Market

ABT-492 is broad-spectrum anti-infective agent with potential application across a broad range of indications, including respiratory infections, genito-urinary infections, and skin/soft tissue infections. It is assumed that a pediatric formulation would not be a part of the primary development plan due to the known adverse events caused by quinolones in pediatric populations. Nonetheless, reports of quinolone pediatric development has been reported (gatifloxacin), hence the pediatric market should be regarded as a potential upside for this quinolone should its safety profile merit its use in pediatrics.

CONFIDENTIAL
JH 008180

KLOTZ DEPOSITION EXHIBIT 19

D'S EXHIBIT 807 – PART 2

Current Treatment Options

Class	Mechanism of Action	Comments
Penicillins	Cell wall synthesis inhibitor	Mostly generic, class has seen significant decrease as a result of penicillin resistance
Cephalosporins	Cell wall synthesis inhibitor	Some generic, class has seen significant decrease in use as a result of prevalence of B-lactamase producing strains and modification of penicillin-binding proteins.
Tetracyclines	Protein synthesis inhibitor	Generic agents, relatively high levels of resistance but are still useful in some indications
Sulfonamides	Folic acid synthesis	Generic agents, relatively high levels of resistance but are still useful in some indications
Macrolides	Protein synthesis inhibitor	Widespread use in RTI, macrolide resistance has been increasing rapidly, but has not yet translated into declines in clinical efficacy; *H. flu* activity continues to be class weakness, along with GI adverse events, drug-drug interactions, & taste perversion
Quinolones	DNA synthesis inhibitor	Fastest growing antibiotic class, used in a broad spectrum of indications; class historically associated with poor Gram+ pathogen coverage and sub-optimal safety profiles; newer agents (Levaquin, Tequin, Avelox) have improved dramatically along both spectrum and safety dimensions.
Oxazolidinones	Protein synthesis inhibitor	Newest antibiotic class to reach market, due to limited Gram– profile will be used primarily in nosocomial setting

U.S. Market
1999 U.S. antibiotic prescription and sales data are presented in the table below.

			1995	1996	1997	1998	1999	$CAGR_{95\text{-}99}$
U.S.	TRXs (MM)	Tab/Cap	220	215	211	208	221	0.1%
		Oral Susp.	76	66	63	59	61	-5.3%
		I.V.	NA	NA	NA	NA	NA	NA
	Sales ($MM)	Tab/Cap	$4,057	$4,220	$4,467	$4,848	$5,715	8.9%
		Oral Susp.	$1,075	$979	$977	$1,001	$1,120	1.0%
		I.V.	$1,865	$1,829	$1,855	$1,890	$2,117	3.2%

Tab/cap and oral suspension prescriptions had been declining 1-2% per year in the period of 1995-1998, presumably from increased attention to appropriate prescribing in the face of increasing resistance; however, prescriptions recovered in 1999, though this may be explained at least in part by a relatively late 1998-99 flu season. Even in the face of this negative pressure on antibiotic use, however, sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics; during 1995-1999, generic tab/cap prescriptions declined by 30MM. So while negative pressure on the use of these antibiotics continues, it appears the market is willing to bear higher costs for agents that meet unmet need. The IV market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

CONFIDENTIAL
JH 008181

Quinolones have seen dramatic growth, with oral and IV sales growing at 17% and 16% compound annual rates, respectively, from 1995-1999. This growth is a function of the newer quinolones successfully penetrating the RTI segment, which was initiated with the1997 launches of Levaquin and Trovan (withdrawn) and continues with the recent introductions of Tequin and Avelox.

Ex-U.S. Market

Ex-U.S. sales of antibiotics totaled $11.7 billion in 1999. The tab/cap represents the largest segment, with sales of $9.4 billion on 770 MM TRX. TRX growth has been flat, with a 1996-99 CAGR of 0.5%; the use of antibiotics is predicted to slowly decline due to more judicious use of antibacterials in the face of increasing bacterial resistance.

Ex-US, the quinolone class accounted for 8% (62MM) of total tab/cap market prescriptions and 13% of sales ($1.2 billion). Ciprofloxacin is the market leader ex-US, with approximately 47% of the quinolone market Rxs (29MM) and 44% ($530MM) of sales. Levofloxacin launched in many European markets in 1998/1999 and holds approximately 14% Rx share of the European quinolone market, and 0.8% of the overall tab/cap market. Although grepafloxacin and trovafloxacin also launched in some European countries in 1999, both products were recently pulled from the market due to liver toxicity and other complications. Moxifloxacin launched in Germany in Q4 1999, but has not yet been approved in other markets. In Japan, levofloxacin launched in 1994 and still commands a 65% Rx share of the quinolone market and 10% of the Japanese tab/cap market overall. Japan accounts for approximately 80% of ex-US levofloxacin sales ($370MM).

	1999 Ex-US Tab/Cap Market					
Class	Sales ($MM)	Sales Share	Sales CAGR '96-'99	TRXs (MM)	TRX Share	TRX CAGR '96-'99
Market	$9,348	--	3.6%	770	--	0.8%
Quinolone Class	$1219	13%	-12%	62	8%	NA
Cipro	$530	5.7%	4.9%	29	3.8%	NA
Levaquin	$466	5.0%	NA	18	2.3%	NA
Trovan	$12	0.1%	NA	0.5	0.1%	NA

Competition

The anti-infective pipeline is very competitive, but most of the competition is focused on improving the activity and safety of the quinolones. Ketolide development is the only other area of activity which is in late stage of development. The quinolone compounds in present development may fall out because of safety or lack of activity against resistant pathogens.

Competitive Analysis – Emerging Competition					
Product	*Company*	*Class*	*Phase/Estimated Time to Market*	*Country*	*Comment*
Ketek (telithromycin)	Aventis	Ketolide	Filed 3/00 Est. launch 3/01	U.S.	Respiratory indications; filed NDA 3/00; 800 mg QD; first in ketolide class to reach market.

CONFIDENTIAL
JH 008182

Competitive Analysis – Emerging Competition					
Product	***Company***	***Class***	***Phase/Estimated Time to Market***	***Country***	***Comment***
Factive (gemifloxacin)	SKB	Quinolone	Filed 12/99 Est. launch 12/00	US	Superior to quinolones for MRSA; highly potent vs. RTI pathogens *H. flu*, *M. cat*, and *S. pneumo* and UTI pathogens *E. coli* and *P. mirabilis*, CRSP; potency > spar, trov, grepa and ≥ moxi; activity vs. *P. aeruginosa*?; good atypical and mycoplasma coverage; intracullular penetration; low photo/CNS tox; 700 patient database
Sitafloxacin	Daiichi Seiyaku	Quinolone (IV only)	III II Est. launch 2002	Japan U.S., Europe	Very potent MRSA, pseudomonas and bacteroides activity; diarrhea, ALT, low WBC; will likely be target to severe rather than community infections
Ecenofloxacin	Chiel Foods	Quinolone	II Est. launch 2002	UK	Active against UTI and RTI pathogens; superior to lome and oflo vs. *P. aeruginosa*. $T_{1/2}$ = 14-19 hr; will likely be target to severe rather than community infections
CS-940	Sankyo	Quinolone	II Est. launch 2002	Japan	Active against G+/-; excellent activity against *H. flu*, *c. jejuni*, *M. pneumo*, and *C. trachomatis*; greater potency than cipro; $t_{1/2}$ ~7 hr; BA~80%
T-3811	Toyama/BMS	Quinolone	I Est. launch 2005	Japan	Excellent potency and low toxicity
DC-756	Daiichi Pharma	Quinolone	Pre-clin Est. launch 2006	Japan	Low toxicity; in vitro potency ≥ trova, STFX & HSR-903

Unmet Needs

Overall unmet need in the anti-infective market is low. Resistance represents the largest unmet need, which will continue to evolve over time. Satisfaction with other product attributes, such as convenience, spectrum of activity, and tolerability/safety is quite high. Any improvements in these areas will be incremental and will offer little in the way of differentiation.

ABT-492 is one of the most active agents against the resistant organisms. It has indications that will have a low propensity for the development of resistance. ABT-492 will be developed to maximize any opportunities to shorten therapy. ABT-492 was chosen from hundreds of quinolones because of its potential to be well tolerated and safe in humans. ABT-492 will have few interactions with other drugs.

Unmet Need	***Pipeline Impact***
Activity against resistant organisms	*Strep. pneumo*, MRSA, and VRE represent most problematic pathogens although new quinolones/ketolides do well with most resistant *Strep. pneumo* strains; quinolone-resistant *Strep. pneumo* may develop; pseudomonas resistance is also increasing; resistance will likely continue to be a source of unmet need due to its dynamic nature.
Low propensity for resistance development	Given that most compounds in development are from classes of drugs already in use, this need is largely unmet. Unclear how quickly resistance will build to new classes of drug; gatifloxacin claims 8-methoxy functional group results in lower propensity for resistance development
Convenience (duration/frequency)	Standard moves toward 5-7 days of therapy with QD dosing; may start to see 3-day therapies for some indications (AECB)
Increased tolerability	While some degree of unmet need exists, increasingly, agents (which have not been withdrawn) are reaching the marketplace with adverse event profiles that approach clinical insignificance; a very clean safety

	profile should be regarded as a necessary component rather than a differentiating one
Few drug-drug interactions	Quinolones, macrolides, and ketolides all interact with other drugs to varying degrees; a potent drug with no interactions would be a benefit in this market

Considerations

Product Usage: Physicians are likely to use ABT-492 for the sicker patients with the most difficult infections to treat. In the outpatient arena it will be used to treat community-acquired pneumonia and acute bacterial excerbations of chronic bronchitis in the older patients with an underlying illness. It will also be used in the hospital for the community-acquired pneumonia patient who requires hospitalization and for serious nosocomial infections.

While many regard quinolones as agents that should be reserved for 2nd line use, their activity against *H. influenzae* and resistant *Strep. pneumoniae* (which current macrolides do not offer) have resulted in a high level of acceptance for empiric 1st line use. The improved safety profiles of several recent quinolones have facilitated their use as 1st line agents. Provided that ABT-492 is proven to have a benign safety/adverse event profile, it will likely receive usage in both 1st-line (non-severe) and 2nd-line (severe) infections.

Side Effects: The quinolone class has potential prolongation of the QT interval and other cardiovascular effects. There is also increased regulatory scrutiny due to recent quinolone withdrawals from international markets. ABT-492 has been evaluated in the standard *in vivo* models used to evaluate QT interval potentials of other antibiotics and has shown no evidence of increasing QT. Also, compared to marketed quinolones, preclinical studies show no evidence or no increase incidence of CNS drug concentration (ie. less potential for dizziness); phototoxicity; and liver toxicity.

Off-label use: It is difficult to predict at this time what off-label uses will be seen for this compound. Initial development will be for the more common respiratory, urinary tract, skin, and hospital infections. Other indications will be evaluated after the primary approval of this compound. Many of the secondary indications will get usage before we have regulatory approval.

COGS: The initial cost of goods is in $6000/kg range, but will come down rapidly after the initial starting materials are determined. At time of launch ABT-492 will have a cost of goods in the $1500/kg range which is competitive compared to other quinolones and other new antibiotics.

Dosing: Based on animal models and the *in vitro* activity of ABT-492 the dose for most oral indications will be in the range of 100 to 200 mg give once daily.

Development/Regulatory: Anti-infective compounds are well understood by regulatory agencies globally and they have clearly defined clinical development path and regulatory guidelines for reference. Abbott Laboratories has been in this arena for many years and has experience with the FDA and European regulatory agencies and so the hurdles to development are well known. ABT-492 has begun but not yet completed its first Phase I study in healthy volunteers.

Other Approaches: Because of the well defined development guidelines there are not many options. The major development options are in dosing regiments. ABT-492 is a very potent drug which has demonstrated rapid killing of pathogens *in vitro* and *in vivo*, and the development plan will attempt to shorten treatment durations to increase the competitive advantages of this activity.

CONFIDENTIAL
JH 008184

Pricing: The community infection market is quite competitive from a pricing standpoint, with recent quinolones priced at approximately $45 per 5-7 days of therapy. The pricing strategy will depend on strengths/weaknesses of the ABT-492 product label, the competitive landscape at launch, and the managed care environment, but current pricing assumption is parity for ABT-492 with respect to other quinolones.

CONFIDENTIAL

ABT – 510

Descriptive Memorandum

February 2001

Abbott Laboratories

ABT 510

Overview

There is abundant evidence that primary tumor growth and metastatic progression require new blood vessel formation (angiogenesis). Tumors secrete inducer proteins including bFGF and VEGF that activate microvascular endothelial cells (EC) causing them to proliferate, migrate and organize into capillary structures. Activated endothelial cells also enhance malignant progression by producing signal molecules (cytokines) that inhibit programmed cell death (apoptosis) of tumor cells. Since anti-angiogenic therapy targets genetically stable endothelial cells, resistance typically seen following cytotoxic chemotherapy is not observed. Moreover, angiogenesis inhibitors should not have the intrinsic toxicity of anti-proliferative chemotherapy. Angiogenesis is also a feature of several other pathophysiologic states of large unmet medical need (macular degeneration, psoriasis, and arthritis, among others).

Angiogenesis sustains the growth and progression of tumors. Unlike chemotherapy or radiation, both of which can damage normal cells in addition to tumor cells, anti-angiogenic agents are hypothesized to prevent growth of new blood vessels and to disrupt critical tumor survival signals produced by EC. These agents may keep tumors in a dormant state for as long as the compound is administered and tumor regressions may occur. Proof of this principle has been demonstrated in pre-clinical models. Currently, at least thirteen compounds with anti-angiogenic activity in cancer are in various phases of clinical development, however few act directly and specifically on the angiogenesis process. Anti- angiogenesis drugs are not expected to replace or compete with current therapies. Instead, if these agents prove to be effective, it is believed that they will be used as supplemental therapy to prevent metastasis following surgery, cytotoxic chemotherapy or radiotherapy. As for cases where tumors have already metastasized, these agents could slow down disease progression and maintain "disease dormancy".

Thrombospondin-1 (TSP-1) was the first natural angiogenesis inhibitor to be discovered. TSP-1 is a large, multifunctional protein. TSP-1 rapidly inhibits EC migration and increases EC apoptosis through activation of caspase-3-like proteases. The normal tissue expression of TSP-1 limits inappropriate neovascularization, however it is transcriptionally activated by the tumor suppressor gene product p53. Therefore, TSP-1 is down-regulated and under-produced in p53 defective tumors. In rodent models, ectopic overexpression of TSP-1 inhibits the malignant phenotype as does direct administration of TSP-1 in the circulation. However, direct clinical use of TSP-1 is not feasible because of its scarcity, large size and multiple other biological functions.

The angiogenic activity of TSP-1 has been localized to the 50,000 MW N-terminal stalk region of this protein, and more specifically to the properdin (Type-1) repeats within this region. Although small synthetic peptides within this region have only weak antiangiogenic activity, it was discovered that a single D-amino acid replacement in a properdin region peptide led to an increase in activity of greater than 1000-fold. ABT-510 is a parenterally available nonapeptide. Although ABT-510 competes with TSP-1 for binding to the EC, the exact mechanism of anti-angiogenesis is unknown.

ABT 510 is supplied for clinical use as a sterile solution in acetate salt in 5% dextrose. ABT 510 is soluble and stable in water.

In vitro, ABT 510 inhibits chemotactic VEGF/bFGF-stimulated migration of human microvascular endothelial cells (EC) with an IC50 of approximately 0.250 nM. This effect is EC specific. ABT-510 (10mg/kg/day subcutaneously) blocks VEGF-induced corneal vascularization in mice. It potently and selectively competes with TSP-1, binding the CD 36 receptor.

CONFIDENTIAL
JH 008187

ABT 510 inhibits tumor progression in vivo. ABT 510(20mg/kg/day subcutaneous administration) inhibited tumor progression (78% growth inhibition at day 38) in a model of human breast cancer (MDA-MB-435) growing in the breast pads of nude mice. Dose dependent inhibition of B16F10 melanoma lung metastases was observed in a second murine model. ABT 526, a molecule highly similar to ABT 510 (which was not advanced into human trials because of concatemer formation) was administered to 23 companion dogs (25mg SQ BID) with sporadic cancers (head and neck carcinoma, lymphoma, sarcoma, etc) refractory to conventional chemotherapy. Surprisingly, 2 complete responses, 5 partial responses (>= 50% shrinkage) and 6 cases of disease stabilitization were observed.

Assays for toxicity, histamine release, hemolysis, T-cell function neutrophil migration, platelet aggregation, receptor (CEREP) screening and CNS function were unremarkable. ABT-510 produced no physiologically significant changes in cardiovascular or hemodynamic function in anesthetized dogs. In addition, there were no physiologically significant changes in clinical blood chemistry profiles or cardiac electrophysiologic function in response to ABT-510. Doses that were many times higher than the predicted efficacious concentration produced a moderate reduction in mean arterial blood pressure in conscious monkeys. ABT-510 was not mutagenic in the Ames assay. It is concluded therefore that ABT-510 has an excellent pre-clinical safety profile.

ABT-510 is currently in Phase I clinical trials. Because of its exceptional safety profile, normal volunteers are being dosed with ABT-510 to establish human safety and pharmacokinetic parameters. Review of these data will lead to a Go/NoGo decision for Phase II trials in the Summer of 2001.

The market

Cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market. The market for products to treat cancer is changing rapidly. It is a growing market fueled by:

- Increasing disease incidence
- New product entries
- New therapeutic paradigms
- A growing adjunctive market, which increases the number of patients eligible for chemotherapy
- Intense research and competition

The increase in the aging population in developed countries increases the incidence of cancer. The diagnosed cancer incidence and prevalence in seven major markets, including the U.S., France, Germany, Italy, Spain, U.K. and Japan are close to 3 million and 10 million respectively. The numbers are increasing steadily. Currently, about one-third of the new medicines in development are targeted against cancer.

Cancer is not a single disease, but includes more than 100 different disorders, which have at their core uncontrolled cell growth. Of these disorders, the cancer types that offer the greatest commercial opportunity include breast, colorectal, lung, ovarian and prostate (based on incidence/prevalence/unmet need). Treatment of breast, lung and prostate cancers account for more than 50 percent of the direct medical costs of cancer therapies. Other cancer types, specific to one or more of the major international markets, may provide niche opportunities. For instance, stomach (gastric) cancer is relatively common in Japan but not in the U.S. or Europe; similarly, liver cancer has a greater occurrence in Japan, Italy and Spain.

CONFIDENTIAL
JH 008188

Depending on tumor type, cancer can be treated with surgery, radiation, chemotherapy (cytotoxic), hormonal therapy or a combination of any of these. For the purpose of this analysis, we will define the cancer market as chemotherapeutics and the adjunctive therapies used to counter the effects of chemotherapy and radiation therapy. The following charts summarize the global sales for these products.

Global Sales by Market Segment ($ MM)

	1996 Sales	1997 Sales	1998 Sales	CAGR '96-'98
Hormone	4,414	4,784	4,884	5.2%
Cytotoxic	4,278	5,212	6,268	21.0%
Adjunctive	3,367	3,651	4,166	11.2%
Total	12,059	13,647	15,318	12.7%

Source: Datamonitor

Sales by Region ($ MM)

	1996 Sales	1997 Sales	1998 Sales	CAGR '96-'98
US	5,564	6,276	7,422	15.5%
Ex- US	6,495	7,370	7,896	10.3%

Source: Datamonitor

Chemotherapeutic agents

Cytotoxic therapies include classes such as alkylating agents, anti-tumor antibiotics, anti-metabolites and antimitotics (taxanes). These agents are toxic and demonstrate dose-limiting side effects. The commercial value of this segment is significantly understated, as most of the products are available in generic form.

The growth of the cytotoxic segment in the past three years has been driven primarily by the introduction of new, more effective and expensive therapies such as Taxol (paclitaxel/BMS), Gemzar (gemcitabine/Lilly), Taxotere (docetaxel/RPR) and Hycamtin (topotecan/SB). Utilization of these newer agents, however, appears to be dependent on the cost sensitivity of the local market. For example, secondary sources indicate that Taxol has recorded over 60% of its global sales in the US market alone and is prescribed with far less frequency in the more cost sensitive UK, German and French markets.

Most chemotherapeutic agents are indicated for just one or two cancer types, but get significant off-label use once approved. Up to 60% of an oncology product's use is potentially for off-label indications. Much of this use is driven by the publication of data and/or approvals in other countries.

Hormonal therapies

Of the top-selling drugs in each major geographical region, *hormone therapies* contribute approximately one-third of the sales ex-US and one-fourth in the US. Hormone therapies for the treatment of cancer include Lupron (leuprolide/TAP), Zoladex (goserelin/Zeneca), Nolvadex (tamoxifen/Zeneca) and other agents used to treat hormone responsive diseases such as prostate and breast cancer. These agents are generally administered chronically and have reduced side effects compared to cytotoxic therapies. Sales of this category are driven primarily by Lupron and Zoladex. The US market has become increasingly cost sensitive in the Medicare sector, which accounts for over 70% of Lupron sales.

Adjunctive agents

CONFIDENTIAL
JH 008189

The availability of effective *adjunctive agents* also allows the cytotoxic chemotherapeutic agents to be administered at higher doses and/or more frequently, or used in a more palliative role, since the adjunctive therapies can reduce the impact of the chemotherapy on the patient's quality of life. Agents in this class include immunostimulants, anti-emetics and bisphosphonates. The growth of this market is linked to the growth of the cytotoxic market, as the increased use of cytotoxic agents drives an increased use in adjunctive therapy. The highest selling product in this class is Neupogen (filgrastim/Amgen) with 1998 sales of over $1 billion.

Biologic Therapy

New therapies under development offer the promise of fulfilling several unmet needs in the treatment of cancer. Experts have predicted that in the future early therapy for breast cancer will be dominated by biological approaches, such as monoclonal antibodies (Herceptin/Genentech), which is widely thought to have strong market potential. Genentech recently reported strong second quarter sales of the product in the US of $46.2 million, and it is estimated that if only half of US women with breast cancer who over-express this gene received Herceptin, sales would top $600 million. In addition to monoclonal antibodies, other biological approaches include vaccines and gene therapy.

Future Trends

Emerging science in the past decade offers the potential to radically alter the paradigm for cancer therapy and presents opportunities for fundamentally new ways of approaching the disease. New therapies offer the promise of fulfilling several unmet needs in the treatment of cancer. These include matrix metalloproteinase inhibitors (MMPIs), continued expansion of biologics, photodynamic therapies (PDT), anti-angiogenics, and multiple drug resistance (MDR) modifiers. This market does not yet exist, though success of "cytostatic-like" treatments, such as hormonal therapies for prostate and breast cancer, suggests that the market potential for cytostatic agents could be significant.

Competition

The angiogenesis pipeline is very competitive, but this level of intensity is somewhat skewed by the large number of mechanistic approaches that are being claimed to demonstrate angiogenic activity. Furthermore, clear evidence of efficacy for these agents has not yet been demonstrated. For the purposes of this summary, only those compounds considered true anti-angiogenic compounds have been included. Companies with compounds in clinical development include Genentech, Entremed, Sugen, TAP, Magainin and Pharmacia Upjohn.

Angiogenesis Compounds in Clinical Development

Compound	Indications	Company	Phase
Neovastat	Solid tumors	Aetema	III
RhuMab VEGF	Cancer	Genentech	II/III
Vitaxin	Arthritis, psoriasis, CVR	Ixsys	II
SU-5416	Cancer	Sugen	II/III
TNP 470	Cancer, arthritis	TAP	II
Thalidomide	Cancer	EntreMed/BMS	I
Squalamine, squalus	Cancer	Magainin	I
RPI 4610	Cancer	Ribozyme	I
VEGF antagonist	Cancer, retinopathy	NeXstar	I
Angiostatin/Endostatin	Cancer	EntreMed	I

CONFIDENTIAL
JH 008190

Unmet Needs

Cancer remains the second leading cause of death in the United States, Europe and Japan, and consequently, offers an attractive market opportunity for the pharmaceutical and biotechnology industries. This year about 563,100 Americans are expected to die of cancer, more than 1,500 people a day. In the US, 1 or 4 deaths is due to some form of cancer. In 1999, about 1,221,800 new cancer cases are expected to be diagnosed.

For most cancers, the level of physician satisfaction with current therapies is low. It has long been recognized by researchers, physicians, patients and family members that current treatment options may often be as devastating as the underlying disease.

Unmet needs in this market vary by tumor types and stages, with some tumors responding to treatment with better mortality and/or morbidity results than others. However, cancer is still treated as a terminal illness with significant shortcomings in present treatments. In general, unmet needs include:

Need	ABT-510 Attribute
Enhanced efficacy of therapeutic agents	Potential for enhanced efficacy
Reduced toxicity	Potential for reduced toxicity over current cytotoxic treatment
Improvements in drug administration	TBD
Improved target delivery of cytotoxics and novel therapeutics	Unknown
Proven outcomes data	Quality of Life and Pharmacoeconomics to be assessed

Considerations

Product Usage: Physicians have indicated that they would use anti-angiogenic agents initially in their more refractory patients, as follow-on or add-on to current best therapy (chemo or surgical). With experience and clinical evidence, they would be willing to use these agents in earlier stages of the disease, where they perceived the greatest benefit to be. Anti-angiogenesis agents are regarded as a maintenance therapy to be used in early disease or after primary therapy as a prophylactic process to prevent the spread of malignancy. Of course, their ultimate use will depend on the benefit provided, which cannot be determined until clinical trials have been completed. Efficacy evidence in humans manifested by tumor response of the magnitude seen in the preliminary dog studies would stimulate tremendous enthusiasm in the oncology community.

Product Benefits/Efficacy: Physicians are looking for improvements in time to tumor progression and prevention of metastases with cytostatic agents. There is a great deal of enthusiasm for this mechanism in the scientific and lay audience. The concept is very intuitive. Products, such as ABT-510, that promise a clinical benefit without the usual toxic trade-offs associated with current chemotherapeutic agents, will be enthusiastically received by oncologists.

Side Effects The proposed safety profile of anti-angiogenic agents may enhance usage, as the dose limiting toxicity profiles of most of the other available agents has established a much lower hurdle for demonstrating a preferred profile. However, as chronic therapy, anti-angiogenic agents may *have* to demonstrate a cleaner profile than cytotoxic agents do to ensure compliance.

Off-label use: Off label use accounts for between 30-60% of an oncology product's usage. Off-label use is driven by publication of clinical trial results in credible journals, listing in key compendia and/or a peer's experience with the product. Therefore, development spend for off-label use is considerably less than the spend required for regulatory approval of an indication. However, promotion of these off-label uses is limited.

Other indications: ABT-510 may be effective in other therapeutic roles, such as arthritic diseases and macular degeneration. These other indications may offer a commercial upside, through internal development or co-development/out-licensing opportunities.

Competition: While there are a relatively large number of angiogenesis inhibitors in development, it is unclear whether they will demonstrate a superior efficacy or side-effect profile vs. ABT-510. The mechanism of angiogenesis suggests that multiple anti-angiogenic approaches may be required to maximize the clinical benefit.

COGS: Initial estimates on finished cost of drug place it in the range of Lupron costs. Depending on final dosing requirements, the cost of this compound could become a significant obstacle. However, this will need to be considered in light of the pricing flexibility in the oncology market, where there is limited pricing sensitivity for products that are reimbursed. Any financial analysis will need to include royalty obligations to Northwestern University.

Dosing: There is still some uncertainty regarding the route of administration and feasible dosage forms for ABT-510. An "inconvenient" formulation leaves this product extremely vulnerable to competitors with more convenient dosage forms. A convenient dosage form, such as a monthly depot, will enhance product adoption over a less convenient form. However, the effect of the various dosage forms on product adoption will be dependent on the benefits the compound provides, side-effect profile and availability of competitive agents with more convenient dosage forms. For chronic therapy, convenience will play an important role in market penetration, given alternative agents. Although less convenient than oral therapy, parenteral therapy (depot, but not self-administered sub-cutaneous) is currently reimbursed by Medicare in the US. Over 60% of all cancer patients have Medicare as their primary healthcare coverage in the US.

Development/Regulatory: With a new class of compounds, there is not a clearly defined clinical development path or regulatory guidelines for reference. This hurdle is similar for all the competitive products, but increases the overall development risk profile for these agents. However, with several anti-angiogenic agents in late stage development, Abbott can learn from their experience.

Other Approaches: Other "cytostatic" approaches may present a competitive threat if they are used as substitutes. Due to the complexity of the pathogenesis of cancer, it is more likely that these agents will be used in combinations, but incremental benefits may become more difficult to demonstrate as the number of products and approaches multiply. This will require additional studies, as these other classes become part of standard cancer treatment. However, this threat is not unique to this compound.

Pricing: The treatment of cancer is expensive, so there is the potential for a great deal of pricing flexibility in this market. There is also an increasing emphasis on cost-effectiveness studies that will need to be addressed in the development plan.

CONFIDENTIAL
JH 008192

CONFIDENTIAL

ABT - 518

Descriptive Memorandum

February 2001

Abbott Laboratories

MMPI

Overview

Abbott's Matrix Metalloproteinase Inhibitor (MMPI) program represents a novel therapeutic class, with the potential to alter the way that cancer is treated by preventing or modifying disease progression and/or metastases. This more "chronic" approach to therapy has the potential to transform cancer into a disease that patients live with, much like the effect of HIV protease inhibitors on patients with AIDS. It also has the potential to expand the cancer market significantly by increasing the average length of treatment and expanding the pool of patients eligible to receive therapy.

The MMPs comprise a family of enzymes that degrade a wide range of matrix protein substrates. High expression of these enzymes occurs in cancer and is associated with the ability of tumors to grow, invade, develop new blood vessels and metastasize.

MMP inhibitors (MMPIs) may suppress the progression of tumors by several mechanisms:

- Suppress invasion/metastasis by blocking the membrane traversal and access to blood/lymphatic vessels
- Blocking the remodeling of extra-cellular matrix in the vicinity of primary tumors to prevent stroma-bound growth factors from stimulating tumor growth
- Blocking angiogenesis by preventing the proliferation and migration of endothelial cells and neovascularization of tumor.

Experimental evidence suggests that gelatinase A and gelatinase B are particularly important in tumor progression, consequently the project team has targeted gelatinase selective inhibitors for the treatment of cancer. Another reason for targeting highly gelatinase selective MMP inhibitors relates to the side effect profile exhibited by broad-spectrum agents like marimastat. Chronic administration of marimastat causes a dose-limiting side-effect characterized by severe joint pain and stiffness. Since these joint effects may be mediated by inhibition of other MMPs like fibroblast collagenase, highly gelatinase selective agents may be efficacious without producing dose-limiting side effects.

The MMP selectivity profile exhibited by ABT-518 distinguishes it from competitor's compounds. ABT-518 possesses sub-nanomolar inhibition potencies versus both gelatinase A and gelatinase B and is substantially more selective for the inhibition of the gelatinases over fibroblast collagenase than marimastat and prinomastat. Despite its high selectivity, ABT-518 demonstrates antitumor activity equal or superior to prinomastat. Inhibition of tumor growth is dose dependent in both syngeneic and xenograft models. ABT-518 is also effective in blocking vessel formation in a mouse model of angiogenesis. ABT-518 is a stable crystalline solid which can be synthesized in six steps (25% overall yield) from commercial starting material.

ABT-518 gives rise to sustained plasma concentrations following single oral dosing in monkeys, dogs and rats. Bioavailabilities range between 68 and 93% depending on formulation and species. Several metabolites are produced after repeated oral dosing of ABT-518, although their relative amounts varies with gender and species.

ABT-518 displays no meaningful effects in genotoxicity, cytotoxicity and ligand binding assays and its cardiovascular effects in dogs are unremarkable. ABT-518 produces no significant toxic effects in rats treated with 100 mg/kg/day over 28 days. Plasma concentrations generated by ABT-518 in these studies are at least 20-fold higher than those necessary to produce efficacy in cancer animal models. ABT-518 is therefore a compelling development candidate with the potential to

CONFIDENTIAL
JH 008194

demonstrate antitumor effects superior to the MMP inhibitors currently undergoing clinical trials. Phase 1 clinical trials in cancer patients began March 2001.

The market

Currently, cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market.

Global Sales by Market Segment ($ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
Hormone	4,414	4,784	4,884	5,000	5.2%
Cytotoxic	4,278	5,212	6,268	7,300	21.0%
Adjunctive	3,367	3,651	4,166	4,900	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

Sales by Region ($ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex- US	6,495	7,370	7,896	8,700	10.3%

Source: Datamonitor

Cytostatic agents have the potential to alter the way cancer is treated and presents opportunities for fundamentally new ways of approaching the disease. This cytostatic market does not yet exist, though success of more cytostatic "like" treatments, such as hormonal therapies for prostate and breast cancer, suggest that the market potential for cytostatic agents could be significant.

The ultimate commercial and clinical success of the MMPI will depend on the clinical benefit this product provides in key cancer types compared with current best therapy. These can be benefits provided by dosing this agent in addition to current therapy and/or as an alternative to best therapy, or as a new component of best therapy. All currently available products, including the market leaders such as Taxol, have significant shortcomings in their profiles.

However, as novel therapy, MMPIs will probably be adopted initially as add-on the current chemotherapy. As benefits are proven and clinical experience is gained, these agents may be used in earlier stages of cancer and/or in conjunction with surgery or radiation to prevent the progression of any microscopic disease that remains.

The clinical targets identified for this compound include late stage pancreatic cancer, late stage NSCL cancer (on-label), with late stage ovarian and breast cancer as additional cancer types where efficacy has been demonstrated, but not filed. Other cancer types this compound may be efficacious in include SCL, colorectal, bladder, stomach and prostate. Targets will be refined as we know more about this compound's in-vivo activity.

CONFIDENTIAL
JH 008195

The following tables summarize the key marketed competitive products by indication (US data only):

Late Stage Breast

Product	Share
Cyclophosphamide/Cytoxan/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	16.25
Paclitaxel/Taxol/BMS	16.11
Trastuzumab/Herceptin/Genetech	11.26

Late Stage NSCL

Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

Late Stage Ovarian

Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/Alza	9.14
Cisplatin/Platinol/BMS	7.58

Late Stage Pancreas

Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Efudex/ICN Pharma	21.0
Leucovorin/	10.7
Cisplatin/Platinol/BMS	4.72

Compounds in Development

The MMP inhibitor field is competitive. More than 30 firms have filed patents claiming small molecule MMP inhibitors over the past 5 years, and several companies have compounds in advanced clinical development. Abbott's compound may be 3rd or 4th to market and will have to demonstrate a competitive advantage to gain the share necessary to support the clinical development of this compound. Companies with compounds in advanced clinical development for the treatment of cancer include Agouron/Warner Lambert/Pfizer, British Biotechnology/Schering Plough and BMS and are listed below. Other companies are targeting this mechanism for arthritis.

Compound	Company	Comments	Phase
Marimistat	BritishBiotechnology/ Schering Plough	Broad spectrum, dose limiting toxicity. Activity seen in gastric cancer, but negative results in pancreatic.	III
Prinomastat	Agouron/ Warner Lambert/ Pfizer	Moderate gelatinase selectivity, dose limiting toxicity. May be dosing sub-optimally to avoid toxicity. Efficacy data not available.	III
BMS 275291	BMS	Broad spectrum, joint effects seen in Phase I studies.	II

Bayer recently dropped development of BAY 12-9566 due to concerns about potential toxicity. Recent results from a study with marimistat in pancreatic cancer, where adding marimistat to Gemzar resulted in no survival advantage, has led to speculation that MMPIs may be more applicable in less aggressive cancer types or earlier stages of the disease. Alternatively, it could be a reflection of the inability to examine higher doses of marimastat due to joint effects.

The joint effects produced by the compounds listed above almost certainly preclude their long-term use, limit compliance and reduce optimal efficacy. Any MMP inhibitor that lacks these side effects will possess a substantial competitive advantage. The musculoskeletal effect produced by marimastat and prinomastat in cancer patients is typically described as arthralgia, myalgia and tendinitis, which occurs predominately in the upper limbs. While mild cases respond to analgesics, interrupting therapy for a period of approximately 2 weeks is necessary when the condition is less well tolerated.

Although Abbott's timing to market is not optimal, the shortcomings of the competitive products provide an opportunity for a compound with an improved SE or efficacy profile. Current animal models seem to predict Abbott's compound is superior to those currently in clinical trials, and has the potential to be best in class.

Product profile

The objective of a product profile at this time in the product's development is to provide a target for the types of attributes that will be required to be commercially successful. This profile is based on market research with oncologists and consultation with opinion leaders. This profile will continue to be refined as more is known about this product's profile, development of competitive products and the market continues to evolve.

CONFIDENTIAL
JH 008197

	Base	Optimal
Efficacy	ABT-518, alone or in combination with best therapy, provides at least one of	Provides more than one of the efficacy benefits outlined.

	the following benefits in at least one solid tumor type: • Increased survival • Tumor regression • Improved quality of life • Increased time to tumor/disease progression	
Competitive advantage	ABT-518 will need to demonstrate a clinically significant advantage in efficacy (see parameters above) or additive synergistic activity with current/competitive agents or clinically significant advantage in side-effect profile relative to other MMPI agents.	Same
Administration	Convenient administration relative to competitive agents.	Same plus reimbursement in US market.
COGS	A finished cost of goods that is consistent with at least an 80% standard manufacturing margin.	A finished cost of goods that is consistent with at least a 90% standard manufacturing margin.

Marketing overview

Product Usage: Physicians have indicated that they would use MMPIs initially in their more refractory patients, as follow-on or add-on to current best therapy (chemo or surgical). With experience and clinical evidence, they would be willing to use these agents in earlier stages of the disease, where they perceived the greatest benefit to be. The MMPI was regarded as a maintenance therapy to be used in early disease or after primary therapy as a prophylactic process to prevent the spread of malignancy.

Product Benefits/Efficacy: Physicians are looking for improvements in time to tumor progression and prevention of metastases with cytostatic agents. The MMPI mechanism has more recently been implicated as having an even more active role in cancer pathogenesis, from preventing primary tumor growth to anti-angiogenic properties. Positive results from competitive agents, such as marimistat in gastric cancer, provides proof of principle for this mechanism.

Side Effects: The proposed safety profile of MMPIs (excluding joint toxicity) may enhance usage, as the dose limiting toxicity profiles of most of the other available agents has established a much lower hurdle for demonstrating a preferred profile. However, as chronic therapy, MMPIs may *have* to demonstrate a cleaner profile than cytotoxic agents do to ensure compliance. As the 3rd or 4th MMPI to market, SE hurdles will be even higher for this compound. As a critical Go/No Go decision point, the joint toxicity of this compound will be evaluated in an expanded Phase I multi-dose study.

Dosing: Discovery is currently targeting an oral dosage form. In general, oral therapies are acknowledged by physicians and patients as being more convenient to the patient. Chronic oral dosing may also reduce overall costs, as infusion support products and personnel would not be required, enhancing pharmacoeconomic evidence.

COGS: Initial estimates on finished cost of drug suggest that drug costs will not be significant for this compound

CONFIDENTIAL
JH 008198

Off-label use: Off label use accounts for between 30-60% of an oncology product's usage. Off-label use is driven by publication of clinical trial results in credible journals, listing in key compendia and/or a peer's experience with the product. Therefore, development spend for off-label use is considerably less than the spend required for regulatory approval of an indication. However, promotion of these off-label uses is limited.

Competition: As the 3rd or 4th MMPI to market, Abbott's compound will need to demonstrate a meaningful clinical advantage over compounds that are in more advanced development. Strict Go/No Go criteria will determine if the MMPI can meet these hurdles. If they cannot be met, the compound will not move forward.

Development/Regulatory: With a new class of compounds, there is not a clearly defined clinical development path or regulatory guidelines for reference. This hurdle is similar for all the competitive products, but increases the overall development risk profile for these agents. However, with several MMPIs in late stage development, Abbott can learn from their experience.

Other Approaches: Other "cytostatic" approaches may present a competitive threat if they are used as substitutes. Due to the complexity of the pathogenesis of cancer, it is more likely that these agents will be used in combinations, but incremental benefits may become more difficult to demonstrate as the number of products and approaches multiply. This will require additional studies, as these other classes become part of standard cancer treatment. However, this threat is not unique to this compound.

Pricing: The treatment of cancer is expensive, so there is the potential for a great deal of pricing flexibility in this market. However, as an oral therapy in the US market, there may be additional downward price pressure for this agent. There is also an increasing emphasis on cost-effectiveness studies that will need to be addressed in the development plan.

Dosing: Discovery is currently targeting an oral dosage form. In general, oral therapies are preferred by physicians and patients because of the convenience to the patient. However, this form may not be the best choice for some people who already have certain digestive system symptoms (vomiting, diarrhea, or severe nausea), cannot swallow liquids or pills, or cannot remember when or how many pills to take. Additionally, in the US market there are several unique factors that currently do not favor oral therapies. Novel oral therapies are not currently reimbursed by Medicare, a significant payer for the oncology patient population. Also, 40-60% of a community oncologist's income is generated through the administration of IV drugs. An oral therapy would not be a source of revenue to the physician.

Clinical Studies

Clinical studies across a wide range of solid tumors will be initiated, including but not limited to breast cancer, non small cell lung cancer, ovarian cancer, pancreatic cancer, etc...

Final indications pursued will depend from the results of the phase II studies.

CONFIDENTIAL
JH 008199

CONFIDENTIAL

Farnesyltranserase Inhibitor

Descriptive Memorandum

February 2001

Abbott Laboratories

Overview

The Ras genes were the first oncogenes of mammalian origin to be discovered. Intensive research over the last decade has led to the elucidation of the normal function of cellular Ras protein, the role of Ras mutations in oncogenic transformation, and the identification of molecular targets, such as the enzyme farnesyltransferase, for inhibiting Ras activity. Although the farnesyltransferase inhibitors (FTIs) were initially designed with the intention of inhibiting the posttranslational prenylation, and hence function, of Ras, it is now becoming apparent that farnesylated proteins other than Ras (e.g., RhoB) are also critical for malignant growth and may be the relevant target for inhibition of farnesylation. While it remains controversial whether blocking Ras activity or altering the RhoB prenylation status is the actual function of an FTI, these agents, exemplified by ABT-839 and FTIs in the clinic, exhibit remarkable anticancer activity against a wide variety of tumors in preclinical models. The current FTI program is projected to reach DDC status in January, 2001.

Abbott evaluated one FTI, ABT-839, in normal volunteers, but decided to discontinue development of this drug due to its poor pharmacokinetic profile. Invaluable experience was gained, however, from both the preclinical and clinical studies with this compound. Abbott's second-generation series are novel structures that exhibit significantly improved potency and oral bioavailability.

There continues to be tremendous enthusiasm in the medical community and pharmaceutical industry for this mechanism of action. Farnesyltransferase inhibitors have demonstrated impressive antitumor activity in preclinical models with activity equivalent to or better than that achieved with conventional cytotoxic chemotherapy given at the maximal tolerated dose. These agents appear to inhibit angiogenesis and, consistent with this activity, minimal resistance has been observed in preclinical models. The potential also exists for synergistic activity in combination with cytotoxic chemotherapy.

The market

Cancer remains the second leading cause of death in the US, and consequently is an attractive market opportunity for the pharmaceutical/biotechnology industries. Approximately 40% of all Americans will develop cancer in their lifetime.

The worldwide cytotoxic and hormonal cancer therapies market is highly fragmented with only BMS and Zeneca holding a greater than 10% market share. Although the market is not concentrated, the field is highly competitive with more than 60 companies focused on the cancer research area. The growth of the oncology market is fueled by increasing disease incidence, new product entries, new therapeutic approaches, a growing adjunct therapy market that expands the number of patients eligible for chemotherapy, and intensified research competition. The data in Tables 1 and 2 summarize the value of the current oncology market. A great deal of uncertainty surrounds the concept of cytostatic treatment of cancer. Conceptually it may transform the way cancer is treated, allowing patients longer disease free survival and improved quality of life. However, at this point in development, this paradigm does not exist in cancer. Considering market, clinical and patient dynamics factors, breast, colorectal, prostate and non-small cell lung cancers are the most attractive targets for development.

CONFIDENTIAL
JH 008201

Table 1. Global sales by market segment ($ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est.)	CAGR '96-'98
Hormone	4,414	4,784	4,884	5,000	5.2%
Cytotoxic	4,278	5,212	6,268	7,300	21.0%
Adjunctive	3,367	3,651	4,166	4,900	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

Table 2. Sales by region ($ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est.)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex-US	6,495	7,370	7,896	8,700	10.3%

Source: Datamonitor

Cytostatic agents have the potential to alter the way cancer is treated and presents opportunities for fundamentally new ways of approaching the disease. This cytostatic market does not yet exist, though success of more cytostatic "like" treatments, such as hormonal therapies for prostate and breast cancer, suggest that the market potential for cytostatic agents could be significant.

The ultimate commercial and clinical success of the FTI will depend on the clinical benefit this product provides in key cancer types compared with current best therapy. These can be benefits provided by dosing this agent in addition to current therapy and/or as an alternative to best therapy, or as a new component of best therapy. All currently available products, including the market leaders such as Taxol, have significant shortcomings in their profiles.

However, as novel therapy, FTIs will probably be adopted initially as add-ons to current chemotherapy. As benefits are proven and clinical experience is gained, these agents may be used in earlier stages of cancer and/or in conjunction with surgery or radiation to prevent the progression of any microscopic disease that remains.

The clinical targets identified for this compound include late stage pancreatic cancer, late stage NSCL cancer (on-label), with late stage ovarian and breast cancer as additional cancer types where efficacy has been demonstrated, but not filed. Other cancer types this compound may be efficacious in include SCL, colorectal, bladder, stomach and prostate. Targets will be refined as we know more about this compound's in-vivo activity.

The following tables summarize the key marketed competitive products by indication (US data only):

Late Stage Breast

Product	Share
Cyclophosphamide/Cytoxan/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	16.25
Paclitaxel/Taxol/BMS	16.11
Trastuzumab/Herceptin/Genetech	11.26

CONFIDENTIAL
JH 008202

Late Stage NSCL

Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

Late Stage Ovarian

Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/Alza	9.14
Cisplatin/Platinol/BMS	7.58

Late Stage Pancreas

Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Efudex/ICN Pharma	21.0
Leucovorin/	10.7
Cisplatin/Platinol/BMS	4.72

Emerging science within the past decade has radically altered the paradigm for cancer therapy and presents opportunities for fundamentally new ways of approaching the disease. Abbott has multiple discovery cytostatic targets, which may improve effective, but we are not alone: more than 200 compounds from other players are in development. The goal of cytostatic therapy is to improve quality of life, controlling the disease and transforming aggressive treatment to a chronic condition, which has been compared to the impact of protease inhibitors on the course of HIV.

Clinical Studies

Considering all the factors, market, clinical and patient dynamics, breast, colorectal, prostate and non-small cell lung cancer appear to be the most attractive targets for development. The development of cytostatic agents faces a number of challenges as regulatory agencies and physicians evaluate the new emerging paradigm of cancer therapy.

Despite the enormous medical need, drugs for chronic treatment/disease stabilization and improved quality of life for cancer patients do not yet exist. Correspondingly, animal models test efficacy that has not yet been validated as predictive of response in humans. Medical oncologists have historically depended on determination of maximum tolerated dose and response manifested by tumor shrinkage for cancer drug development. These parameters are not relevant to novel "cytostatic" agents. Combination with conventional cytotoxic drugs will be required in the near term and will have to be determined empirically. Intermediate and surrogate measures of biological response will have to be developed. Regulatory agencies are grappling with the same issues.

CONFIDENTIAL
JH 008203

Competition:

Within Project Approach

Company	Compound	Indication	Status of compound	Status of project
Janssen Pharmaceutica	R-11577 (A-251076)	Cancer (unspecified)	Phase III	active
Schering-Plough	Sch66336 (A-285622)	Cancer (unspecified)	Phase II	active
Merck	L-778123	Cancer (unspecified)	Phase I (i.v.) abandoned	unknown
Bristol-Myers Squibb	BMS-214662	Cancer (unspecified)	Phase I	active
LG Chemical	LB 42908	Cancer (unspecified)	preclinical	active
Rhône-Poulenc Rorer	quinuclidine derivatives	Cancer (unspecified)	preclinical	active
Pfizer	unknown structure	Cancer (unspecified	preclinical	active
Parke-Davis	unknown structure	Cancer (unspecified)	preclinical	active
Roche	peptidomimetics	Cancer (unspecified)	preclinical	abandoned project
Eisai	peptidomimetics	Cancer (unspecified)	preclinical	abandoned project
Banyu	FPP mimetic	Cancer (unspecified)	preclinical	unknown
ISIS	ISIS-2503 (ras antisense)	Cancer (unspecified)	Phase I	active

Within Therapeutic Area

Approach	Selected Compounds	Company(ies)	Status
antisense	ISIS 3521, ISIS, 5132	ISIS	phase I
cytotoxic agents	camptosar, CI-980, farestron, Genzar, Hycamtin, Indarubcin, Novantrone, Onconase, Capecitine, Tomudex	P&U, Warner-Lambert, Schering, Lilly, SKB, P&U,Immunex, Alfacell, Roche, Zeneca	most phase III
differentiation	targretin, panretin, 5-azacytidine	Ligand, NCI	Ligand in phase II/III
drug resistance modifiers	VX-710, 776C85, RMP-7, CT-2584	Vertex, Glaxo Wellcome, Alkermes, Cell Therapeutics	Vertex in phase II
gene therapy	Onyx-015, , MDRx1, GLI-328, IL-2, GV-1301	Onyx, Introgen, Therion Biologics, Theragen, Genetic Therapy, Cyclacel, RPR Gencell, GeneMedicine, Titan, etc	Restricted to accessible cancers. Most advanced: Phase I/II
hormonal therapy	Zolodex, armidex, droloxifen, Oncolar, Rivizor, Casodex, rogletimide	Zeneca, Pfizer, Novartis, Janssen, US bioscience	most phase III
immunotherapy			
antibodies	IDEC-Y2/In2B8, anti-HER2, anti EGFR	IDEC, Genetech, ImClone	IDEC recently approved, others phase III
cytokines	IL-12, IL-4, Proleukin, Roferon-A	Roche, Schering, Chiron, Roche	phase III
vaccines	rV-gp100, Genevax, MGV	Apollon, Therion, Progenics	phase I, II
photodynamic	photofrin, promycin	QLT photo, Vion	phase III
radiation sensitizers	Neu-Sensamide, radinyl	Oxigene, Roberts	phase II, III
metalloproteinase inhibitors	marimastat, AG-3340, CGS-27023A	British Biotech, Agouron, Novartis, Bayer	BBT in phase III
angiogenesis inhibitors	TNP-470, SU-5416, anti VEGF-mAb, thalidomide, DC101	TAP, Sugen, Genentch, Entremed, ImClone, etc	see angiogenesis project review for details

CONFIDENTIAL
JH 008204

Competitive Analysis

The project is on par with others in the industry. While second generation Abbott compounds are not yet in clinic, all of the compounds from other companies that are in clinical trials have deficiencies. While the Schering compound has the best oral PK profile, it is not particularly potent. The Janssen compound is potent, but has a poor PK profile. The Merck compound exhibited QTc prologation and development has been stopped. The Bristol Myers Squib compound, BMS-214662, which is in phase I, is an *in vitro* submicromolar inducer of apoptosis in human tumor cells and appears to be the most potent inducer of apoptosis of the known FTIs. This compound could have a different mechanism of action from the classical FTIs and have its own liabilities. LG42908 from LG Chemical is potent FTI and has good oral bioavailability (F= 91% in monkey), however, it's a CYP3A4 inhibitor and will have significant drug-drug interaction liabilities. Extensive preclinical pharmacology at Abbott has defined optimum parameters for a FTase inhibitor that may not be known to our competitors, or be achievable with the current generation of FTIs. Although not yet established, we anticipate that the Abbott compound will be improved over competitors' compounds with respect to potency, oral bioavailability, half-life, toxicity, efficacy, angiogenesis inhibition, and lack of resistance.

CONFIDENTIAL
JH 008205

CONFIDENTIAL

DOPAMINE RECEPTOR AGONIST PROGRAM

Descriptive Memorandum

February 2001

Abbott Laboratories

CONFIDENTIAL
JH 008206

D4 Agonists for Male Erectile Dysfunction

Scientific Overview

Male erectile dysfunction (MED) is defined as the "inability to maintain an erection sufficient for satisfactory sexual intercourse" (NIH Consensus Panel) and results from physiological (organic), psychogenic causes, or a combination thereof. This disorder is associated with decreased quality of life, including personal well being, and diminished family and social relationships. In 1999, an estimated 77 million men over the age of 40 (52% of men over 40 years-old) in the seven major pharmaceutical markets experienced some degree of MED, and the prevalence increases with age. Approximately 10-20% of patients have severe or complete MED, and the majority of the population suffers from moderate disease. While the introduction of Viagra has increased the diagnosis rate of MED in the U.S., 75% or more of patients do not seek treatment. However, as the "baby boomer" generation ages, MED will become a more prominent concern and a growing number of patients are likely to seek treatment.

Abbott's male erectile dysfunction program targeting D4 dopamine receptors represents a novel therapeutic approach to the rapidly growing male erectile dysfunction (MED) market. The current gold standard for the treatment of MED, Viagra. acts peripherally at the penile smooth muscle level to induce erection by modulating the levels of cGMP. In contrast, a selective D4 dopamine agonist will act in the brain at the sites necessary for initiation of a successful erection. Targeting the D4 receptors in brain offers the potential for efficacy in patients with MED that do not respond to Viagra (for example patients with diabetes). Additionally, targeting D4 receptors should not result in any cardiovascular adverse events unlike Viagra which can cause serious cardiovascular effects in patients who are on nitroglycerine-based medications. Since safety is of paramount importance for any life-style disorder like MED, a new agent that does not have any contraindications or warnings related to safety issues may be positioned to become the gold-standard therapy.

Evidence for the potential of a selective D4 dopamine receptor agonist for the treatment of erectile dysfunction includes:

- The non-selective dopamine receptor agonist apomorphine (Uprima™) has been shown to be effective in phase III clinical trials, and has received scientific approval for market in the EU, for the treatment of MED. This validates the utility of dopaminergic agonists to facilitate penile erections in humans. However, the clinical development of apomorphine for the US market has been hampered by dose limiting side-effects (emesis and syncope).

- Studies at Abbott have established that the efficacy of apomorphine (penile erection) and side-effect (emesis) are mediated by different dopamine receptor subtypes. There are 5 known dopamine receptors. Abbott scientists have discovered that the selective activation of D_4 receptors can facilitate penile erection in animals, while the D_2 receptor appears to mediate the emetic effect of apomorphine. The discovery of a D_4 selective agonist maximizes the possibility to identify a compound with equivalent/superior efficacy to apomorphine but devoid of its side-effect liabilities.

PPD is currently screening the Abbott library of compounds to identify novel and proprietary D4 dopamine receptor compounds. Initial hits have been identified that are as potent as any known D4 dopamine receptor agonist. The strategy is to aggressively profile these hits for selectivity across the five different dopamine receptor subtypes and to ensure that selective agents are effective in a number of preclinical in vivo models of MED and have no emetic or cardiovascular side effects. The D4 dopamine receptor agonist program will be discontinued if selective D4 agonists do not achieve at least a 30-fold separation between efficacy in a model of MED and cardiovascular/emetic side effects.

Abbott has a competitive advantage in the race to exploit selective D4 dopamine receptor agonists for MED. A patent application covering the use of any selective D4 agonist for the treatment of MED has been filed and no other pharmaceutical company may have the range of preclinical models of efficacy and safety in addition to access to the clinical information gained from the development of apomorphine. Our molecular modeling group has facilitated advances in the design of selective D4 agonists.

Market Analysis

The introduction of Viagra combined with increased disease awareness resulted in the MED market in the US exploding from \$157MM in 1997 to an estimated \$726MM in 2000. Worldwide, this market has seen similar growth, and is estimated at \$500MM for ex-US for 2000. Viagra currently dominates the MED market, with more than \$1billion in sales in the \$1.3 billion worldwide market in 1999, and >95% of the MED prescriptions in the US. The market growth is expected to continue, with an estimated CAGR in the US of 17.9% (2000 – 2005), fueled by increased awareness of MED, expanded use to wider patient segments for relationship or performance enhancement, and the introduction of heavily promoted new agents. Downward pressure on growth will come from continued perceptions of safety concerns, the limited efficacy of Viagra™, and out-of-pocket cost to patients.

Market drivers influencing the potential of a D4 dopamine receptor agonist include:

- Patient Awareness and Demand Viagra has built considerable awareness of MED. However, in the US, only 10-25% of current MED patients seek treatment for this disorder. Ex-US the percentage of patients seeking treatment is lower (10%). This is mainly due to the lack of DTC promotional campaigns in the ex-US markets. Further market expansion requires continued patient and physician education.

- Product Safety: There are growing patient and regulatory concerns regarding the safety of Viagra. While, physicians currently perceive Viagra™ to be safe, if used by the correct patients, there is significant concern regarding the concomitant use of nitrates for cardiovascular disorders with Viagra. Approximately 10% of Viagra patient deaths have been attributed to use of nitrates. Thus, there is an opportunity to eliminate this concern for physicians and to expand the market.

- Product Efficacy: In clinical trials Viagra allowed successful intercourse in about 50% of attempts. The limited and inconsistent efficacy of the product has resulted in patient dissatisfaction and discontinuation, thus creating a chance to drive Viagra quitters or switchers, as well as new patients, to new, more effective, MED products. The demonstration of efficacy in a broader population of MED patients might also influence physicians to try an alternative product prior to Viagra. The delay in onset (~1hr) and the variability in onset of action from patient to patient is an additional complaint about Viagra. Product features of a selective D4 agonist such as a more rapid onset of action or more reproducible onset will have a positive influence on the market opportunity for MED therapies.

- Additional Indications: Use of a D4 dopamine receptor agon in other indications such as "relationship enhancement" (female sexual dysfunction and age-related decline in male sexual performance) offers an opportunity to both expand the potential market to include women and non-MED sufferers, and reduce the embarrassment of MED for patients. Additional research is required to identify meaningful endpoints in this expanded indication. Initial studies conducted by Pfizer showed that Viagra™ was not effective to treat female sexual dysfunction.

Competitive Overview

The following tables summarize the key competitive activities in regard to marketed products and products in the development pipeline. To date there are no reports any other company targeting selective D4 agonists for the treatment of MED, although a number of companies do have activities in the dopamine receptor arena for other indications that could be re-focused to MED if they became aware of Abbott's insights into the D4 receptor.

A. Oral agents

Approach	Compound/Product	Company(ies)	Status
PDE5 inhibition	Sildenafil (Viagra™)	Pfizer	Marketed
DA receptor	Apomorphine (Uprima™)	TAP	NDA filing withdrawn
Adrenergic	Phentolamine (Vasomax™)	Schering-Plough/Zonagen	NDA filing on hold (>1 year)
PDE5 inhibition	IC351 (Cialis™)	ICOS-Lilly	Phase III
PDE5 inhibition	Vardenafil	Bayer	Phase II-III

B. Intranasal

Approach	Compound/Product	Company(ies)	Status
DA receptor	Nasal apomorphine	Nastech	Phase II

C. Intracavernosal agents

Approach	Compound/Product	Company(ies)	Status
EP receptor	PGE_1 (Caverjet™, Edex™)	Pharmacia, Schwarz Pharma	Marketed
VIP receptor/ Adrenergic	VIP-phentolamine (Invicorp™)	Senetek	Marketed outside US
K channels	PNU 83757	Pharmacia	Phase II

D. Intraurethral agents

Approach	Compound/Product	Company(ies)	Status
EP receptor	PGE_1 (Muse™)	Vivus, Abbott	Marketed

E. Topical

Approach	Compound/Product	Company(ies)	Status
EP receptor	PGE_1 (Alprox-TD; Topiglan)	NexMed; MacroChem	Phase II and III

CONFIDENTIAL
JH 008209

KLOTZ DEPOSITION EXHIBIT 20

D'S EXHIBIT 808

Klotz
EXHIBIT NO. 20
5-16-07
MICHELLE KEEGAN

CONFIDENTIAL

ABT – 773

Descriptive Memorandum

May 2000

Abbott Laboratories

June 5, 2000 Hancock – ABT-773

ABT-773

Opportunity Overview

ABT-773 pertains to a promising new class of antibiotics known as ketolides. ABT-773 is likely to have activity against resistant strains of bacteria and will, therefore, compete effectively against currently marketed antibiotics. The compound is currently in Phase IIb trials. It is scheduled to begin in phase III clinical trials in Q4, 2000 and has an expected U.S. launch date of January 2003. Ex-U.S. launches are projected for 2003 and 2004 for Europe and Japan, respectively.

Product features such as high efficacy, activity against resistant strains of bacteria and convenience should enable it to compete against both Zithromax and newer agents such as the quinolones. Dosing is expected to be once-a-day. A 5-day convenience pak at a competitive price will help maximize sales. Worldwide sales, including tablet/capsule, oral suspension and intravenous (I.V.) forms, are projected to top $1 billion by 2007.

The US Market

The overall antibiotic market in the U.S. reached $8.9 billion in sales in 1999. The tab/cap segment is the largest; sales in 1999 were $5.7 billion. The I.V. and oral suspension segments are comparatively smaller; total sales topped $2.1 and $1.1 billion, respectively.

Tab/cap and oral suspension prescription volume had been declining 1-2% per year in the period of 1995-1998, due to more appropriate prescribing in the face of increasing resistance. However, total tab/cap prescription volume recovered in 1999 and grew 6.3%. Even in the face of negative pressure on antibiotic use, dollar sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics. The market is willing to bear higher costs for agents that satisfy unmet needs. The I.V. market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

Macrolides, largely fueled by the gains of Zithromax, have seen significant growth in terms of both prescriptions and sales. Zithromax prescriptions far outnumber those of other competitors, while its sales have nearly surpassed those of the sales leader, Cipro. Historically, quinolones saw relatively limited use for community respiratory tract infections (RTIs) because of poor Gram-positive coverage and sub-optimal adverse event profiles. Newer quinolones such as Levaquin have been successful in achieving more widespread use by virtue of its improved activity and adverse event profile. Levaquin currently accounts for approximately 30% of quinolone market share. It is anticipated that recent quinolone introductions (Avelox, Tequin) will build upon the RTI momentum established by Levaquin. The growth of the macrolide and quinolone classes has come largely at the expense of cephalosporins and generic agents such as erythromycin and penicillin.

The following table shows 1999 tab/cap sales and prescriptions by class/product:

	Sales			TRXs		
	Sales ($MM)	Share	$CAGR_{95\text{-}99}$	TRXs (MM)	Share	$CAGR_{95\text{-}99}$
Penicillins	$148.3	2.6%	-1.0%	52.5	23.7%	-5.6%
Cephalosporins	$980.9	17.2%	-5.8%	37.9	17.1%	-3.5%
Ceftin	$383.9	6.7%	1.8%	5.0	2.3%	-1.0%
Cefzil	$188.7	3.3%	12.5%	2.7	1.2%	11.3%
Other	$408.3	7.1%	-14.7%	30.1	13.6%	-4.8%
Ext. Spec. Macrolides	$1,595.6	27.9%	19.9%	36.1	16.3%	20.8%
Biaxin	$690.5	12.1%	6.1%	11.3	5.1%	1.2%
Zithromax	$891.1	15.6%	42.1%	24.4	11.0%	41.5%
Other	$14.0	0.2%	21.0%	0.4	0.2%	53.0%
Quinolones	$1,622.1	28.4%	17.0%	24.0	10.8%	11.7%
Cipro	$902.5	15.8%	8.3%	14.1	6.4%	5.1%
Levaquin	$529.4	9.3%	NA	7.0	3.1%	NA
Other	$190.2	3.3%	-2.2%	3.0	1.3%	-6.4%
Augmentin	$778.1	13.6%	17.8%	10.7	4.8%	11.8%
Other Classes	$590.5	10.3%	-1.1%	60.4	27.3%	-4.1%
TOTAL TAB/CAP	$5,715.4	100.0%	8.9%	221.5	100.0%	0.1%

U.S. Market Projections

Resistance to antibiotics is likely to increase, creating opportunities for new agents with activity against resistance. Physicians will be urged to choose agents with an appropriate spectrum of activity relative to the infection being treated. Resistance will increasingly become part of the promotional mix for emerging agents. The ability of an agent to treat resistant strains and the real or perceived ability to slow or prevent resistance development (mutation prevention concentration, low mutation frequency, structure-activity relationships, etc) may confer competitive advantage to such agents.

- Quinolones, which historically have seen limited use in community-acquired respiratory infections, will become a significant class in this segment as new agents from this class are launched that specifically target RTIs.

- The market will become more competitive as new agents enter both the community segment (ketolides, quinolones) as well as the nosocomial segment (oxazolidinones, streptogramins, everninomycins, peptides, others).

- Several key branded antibiotics will lose patent exclusivity over the next three to five years.. This may create an opportunity in the pediatric market as the top three pediatric brands (Augmentin, Cefzil, Zithromax) are among those losing patent exclusivity.

Antiviral influenza and cold therapeutics, as well as an increasing number of antibacterial vaccines may have a negative impact on antibiotic prescriptions.

The Ex-U.S. Market

Ex-U.S. sales of antibiotics totaled $11.7 billion in 1999. Tab/cap represents the largest segment, with sales of $9.4 billion from 770 million total prescriptions. Total Rx growth has been flat, with a 1996-99 CAGR of 0.5%. The use of antibiotics is predicted to slowly decline due to more judicious use of antibacterials in the face of increasing bacterial resistance.

Ex-U.S., the quinolone class accounted for 8% of total tab/cap market prescriptions (62 million Rxs) and 13% of sales ($1.2 billion). Ciprofloxacin is the market leader ex-U.S. with approximately 47% of the quinolone market Rxs (29 million Rxs) and 44% ($530MM) of sales. Levofloxacin launched in many European markets in 1998/1999 and holds approximately 14% Rx share of the European quinolone market and 0.8% of the overall tab/cap market. Although grepafloxacin and trovafloxacin also launched in some European countries in 1999, both products were recently pulled from the market due to liver toxicity and other complications. Moxifloxacin launched in Germany in Q4 1999, but has not yet been approved in other markets. In Japan, levofloxacin launched in 1994 and still commands a 65% Rx share of the quinolone market and 10% of the Japanese tab/cap market overall. Japan accounts for approximately 80% of ex-U.S. levofloxacin sales ($370MM).

Scientific Rationale for ABT-773

The likely profile of ABT-773 justifies further development:

- ABT-773 pertains to a new class of antibiotics.
- Good activity against resistant gram + organisms, particularly macrolide resistant S. pneumoniae.
- Convenience, safety, and tolerability profile competitive with Z-pak.
- Oral Suspension and I.V. forms enabling penetration into pediatrics and hospital segments.

Clinical Studies

The safety and efficacy of ABT-773 in AECB were studied in a multi-center Phase II clinical trial conducted between January and April of 1999. Dosing regimens of 100mg TID and 200mg TID were tested. Of the 169 enrolled patients, 159 were clinically evaluable and 96 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Presumed Bacterial Eradication	ABT-773 100mg TID	ABT-773 200mg TID	Overall Eradication
S. pneumoniae	100% (13/13)	90% (9/10)	96% (22/23)
M. catarrhalis	100% (6/6)	100% (7/7)	100% (13/13)
H. influenzae	96% (23/24)	92% (24/26)	92% (47/50)
H. parainfluenzae	100% (6/6)	88% (7/8)	93% (13/14)

Clinical Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (77/80)	92% (73/79)
Failure	4% (3/80)	6% (3/48)

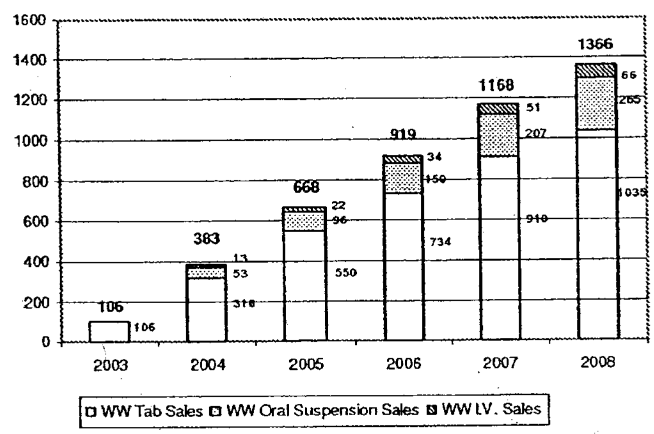
Clinical and Bacteriological Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (46/48)	94% (45/48)
Failure	4% (2/48)	6% (3/48)

Adverse Events	ABT-773 100mg TID	ABT-773 200mg TID	Overall
Taste Perversion	5% (4/84)	8% (7/85)	6.5% (11/169)
Diarrhea	11% (9/84)	6% (5/85)	8% (14/169)
Nausea	2% (2/84)	2% (2/85)	2% (4/169)
Abdominal Pain	1% (1/84)	2% (2/85)	2% (3/169)
Headache	2% (2/84)	1% (1/85)	2% (3/169)
Rash	2% (2/84)	1% (1/85)	2% (3/169)
Dyspnea	2% (2/84)		1% (2/169)
Elev. Liver Funct. Test	1% (1/84)	1% (1/85)	1% (2/169)
Fever		2% (2/85)	1% (2/169)

Patent Status

ABT-773 will have patent exclusivity through 2016.

Financial Projections



Total Worldwide ABT-773 Net Sales by Form ($MM)	2003	2004	2005	2006	2007	2008
US Tablet Sales	64	159	289	383	481	570
US Oral Suspension Sales		41	59	88	123	162
US I.V. Sales		12	18	26	37	48
Total U.S. Sales	64	212	366	497	641	780
Ex-US Tablet Sales	43	157	261	352	430	465
Ex-US Oral Suspension Sales		12	38	63	84	103
Ex-US I.V. Sales		1	4	8	14	18
Total Ex-US Sales	43	170	303	423	528	586
Total Worlwide ABT-773 Sales	106	383	668	919	1168	1366

Assumptions for Financial Projections

- The tab form of ABT-773 launches in the U.S. and ex-U.S. in 2003; I.V. and oral suspension launch in 2004.
- 5 day QD compliance pak available.
- ABT-773 priced competitively with other macrolides, ketolides and quinolones in market at time of launch.
- Efficacy against multi-drug resistant Strep. pneumoniae is main point of differentiation vs. beta-lactam, macrolide and quinolone antibiotics.
- Tolerability equivalent to Zithromax.

- **Appendix 1**

Key Emerging Competitors

Generic	Brand	Company	Class	Status
moxifloxacin	Avelox	Bayer	Quinolone	Approved by FDA 12/13/00
gatifloxacin	Tequin	BMS	Quinolone	Approved by FDA 12/21/00
gemifloxacin	Factive	SKB	Quinolone	Filed NDA 12/15
T-3811	TBD	BMS/Toyama	Quinolone	Phase I
telithromycin	Ketek	Aventis	Ketolide	Filed NDA 3/00
linezolid	Zyvox	Pharmacia	Oxazolidinone	Approved by FDA Q2 '00

KLOTZ DEPOSITION EXHIBIT 21

D'S EXHIBIT 809

Klotz
EXHIBIT NO. 21
5-16-07
MICHELLE KEEGAN

***for Steve to read

1: J Antimicrob Chemother 2000 Feb;45(2):167-73

Macrolide resistance and erythromycin resistance determinants among Belgian Streptococcus pyogenes and Streptococcus pneumoniae isolates.

Descheemaeker P, Chapelle S, Lammens C, Hauchecorne M, Wijdooghe M, Vandamme P, Ieven M, Goossens H

Department of Microbiology, University Hospital Antwerp, Universitaire Instelling Antwerpen, Universiteitsplein 1, B-2610 Wilrijk, Antwerp, Belgium.

Resistance of streptococci to macrolide antibiotics is caused by target-site modification or drug efflux. The phenotypic expression of target-site modification can be inducible or constitutive. The prevalence of the three phenotypes among Belgian erythromycin-resistant Group A streptococci (GAS) and Streptococcus pneumoniae isolates was surveyed, their MICs for seven antibiotics were determined and the clonality of the isolates was explored. Of the 2014 GAS isolates tested 131(6.5%) were erythromycin resistant (MIC > 1 mg/L): 110 (84.0%) showed the M-resistance phenotype whereas the remaining 21 strains (16.0%) were constitutively resistant. No inducibly resistant strains were detected. Of 100 S. pneumoniae isolates, 33 were erythromycin resistant (MIC > 1 mg/L). In contrast to the GAS isolates, only 9.1% of the 33 erythromycin-resistant S. pneumoniae isolates showed the M-resistance phenotype. The presence of mefA/E and ermB genes in the M-resistant and constitutively and inducibly resistant strains, respectively, was confirmed by PCR analysis. Genomic analysis based on pulsed-field gel electrophoresis (PFGE) using the restriction enzyme SfiI, revealed 54 different PFGE patterns among the 131 erythromycin-resistant GAS isolates, of which an M6 clone represented 16.0% of the strains; all other clones, exhibiting different M-types, represented <7% of the strains. The S. pneumoniae isolates also appeared to be polyclonally based, as determined by arbitrarily primed PCR. **The macrolides miocamycin and rovamycin, the lincosamide clindamycin and the ketolide HMR 3647 showed excellent activity against the M-resistant GAS and S. pneumoniae strains.**
(HMR 3647 is a Hoechst Marion Roussel antibiotic. It appears in more than one recent paper as especially promising. Also a number of other antibiotics and types showed excellent activity?)

PMID: 10660498, UI: 20127818

CONFIDENTIAL
JH 002212

***2: Bioorg Med Chem Lett 1999 Nov 1;9(21):3075-80

Synthesis and antibacterial activity of HMR 3647 a new ketolide highly potent against erythromycin-resistant and susceptible pathogens.

Denis A, Agouridas C, Auger JM, Benedetti Y, Bonnefoy A, Bretin F, Chantot JF, Dussarat A, Fromentin C, D'Ambrieres SG, Lachaud S, Laurin P, Le Martret O, Loyau V, Tessot N, Pejac JM, Perron S

Medicinal Chemistry, Hoechst Marion Roussel, Romainville, France.
alexis.denis@hmrag.com

In the search for new ketolides with improved activities against erythromycin-resistant S. pneumoniae and H. influenzae we synthesized a new 11,12 carbamate ketolide substituted by an imidazo-pyridyl side chain: HMR 3647. (*Unlike polyketides, which are made in microorganisms by gene combinatorics, ketolides appear to be synthesized. Are their combinatorial approaches to identify promising candidates?*) **This compound demonstrated a potent activity against erythromycin susceptible and resistant pathogens, including penicillin G/erythromycin A-resistant S. pneumoniae and H. influenzae.** In vivo, HMR 3647 displayed good pharmacokinetic parameters (Cmax = 2.9 microg/ml, bioavailability=49%, AUC0.8 = 17.2 microg.h/l, t1/2=1h) and was shown to have a **high therapeutic efficacy in mice** infected by various respiratory pathogens, including multi-resistant S. pneumoniae and Gram negative bacteria such as H. influenzae. **HMR 3647 appears to be a very promising agent for the treatment of respiratory infections and is currently in clinical trials** (*Abbott doesn't list this in its "key emerging competitors," even though this is a Nov. 1999 article*)
(*Which are the most promising new classes, Quinolones, polyketides, macrolides, ketolides, others?*)
PMID: 10560728, UI: 20023384

3: Antimicrob Agents Chemother 1999 Apr;43(4):930-6

In vitro activities of two ketolides, HMR 3647 and HMR 3004, against gram-positive bacteria.

Malathum K, Coque TM, Singh KV, Murray BE
(*Good interview candidates*)
Center for the Study of Emerging and Re-Emerging Pathogens, University of Texas Medical School, Houston 77030, USA.

The in vitro activities of two new ketolides, HMR 3647 and HMR 3004, were tested by the agar dilution method against 280 strains of gram-positive bacteria with different antibiotic susceptibility profiles, including Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium, Streptococcus spp. (group A streptococci, group B streptococci, Streptococcus pneumoniae, and alpha-hemolytic streptococci). Seventeen erythromycin-susceptible (EMs), methicillin-susceptible S. aureus strains were found to have HMR 3647 and HMR 3004 MICs 4- to 16-fold lower than those of erythromycin (MIC at which 50% of isolates were inhibited [MIC50] [HMR 3647 and HMR 3004], 0.03 microgram/ml;

range, 0.03 to 0.06 microgram/ml; MIC50 [erythromycin], 0.25 microgram/ml; range, 0.25 to 0.5 microgram/ml). All methicillin-resistant S. aureus strains tested were resistant to erythromycin and had HMR 3647 and HMR 3004 MICs of > 64 micrograms/ml. The ketolides were slightly more active against E. faecalis than against E. faecium, and MICs for individual strains varied with erythromycin susceptibility. The MIC50s of HMR 3647 and HMR 3004 against Ems enterococci (MIC < or = 0.5 microgram/ml) and those enterococcal isolates with erythromycin MICs of 1 to 16 micrograms/ml were 0.015 microgram/ml. E. faecalis strains that had erythromycin MICs of 128 to > 512 micrograms/ml showed HMR 3647 MICs in the range of 0.03 to 16 micrograms/ml and HMR 3004 MICs in the range of 0.03 to 64 micrograms/ml. In the group of E. faecium strains for which MICs of erythromycin were > or = 512 micrograms/ml, MICs of both ketolides were in the range of 1 to 64 micrograms/ml, with almost all isolates showing ketolide MICs of < or = 16 micrograms/ml. The ketolides were also more active than erythromycin against group A streptococci, group B streptococci, S. pneumoniae, rhodococci, leuconostocs, pediococci, lactobacilli, and diphtheroids. Time-kill studies showed bactericidal activity against one strain of S. aureus among the four strains tested. **The increased activity of ketolides against gram-positive bacteria suggests that further study of these agents for possible efficacy against infections caused by these bacteria is warranted.**

PMID: 10103202, UI: 99216907

4: Curr Microbiol 1998 Dec;37(6):418-25

Inhibition of translation and 50S ribosomal subunit formation in Staphylococcus aureus cells by 11 different ketolide antibiotics.

Champney WS, Tober CL
(interview candidates)
Department of Biochemistry and Molecular Biology, J.H. Quillen College of Medicine, East Tennessee State University, Johnson City, TN 37614, USA.

Eleven structurally similar ketolide antibiotics were tested at a concentration of 1 &mgr;g/ml for their relative inhibitory effects on growth and ribosome activities in Staphylococcus aureus cells. Ten of the compounds examined had an inhibitory effect on protein synthesis at this concentration and eight of the 11 compounds were also effective inhibitors of the formation of the 50S ribosomal subunit. All of the drugs tested inhibited protein synthesis to a greater extent than they affected 50S subunit formation. The decline in growth rate and cell number was proportional to the effect on ribosome formation and function. The growth of an ermC erythromycin-resistant strain of S. aureus was also significantly inhibited by nine ketolide compounds, suggesting that they were not inducers of methylase gene expression. These inhibitory activities can be

related to structural differences between these ketolide antibiotics.

PMID: 9806981, UI: 99025987

5: J Antimicrob Chemother 1998 Sep;42(3):297-301

In-vitro activity of the new ketolide antibiotic HMR 3647 against gram-positive bacteria.

Schulin T, Wennersten CB, Moellering RC Jr, Eliopoulos GM
(*excellent interview candidates, because of local connection*)
Department of Medicine, Beth Israel Deaconess Medical Center, and Harvard Medical School, Boston, MA 02115, USA.
(*Does Andy Onderdonk know these researchers*)
The comparative in-vitro activity of HMR 3647, a new ketolide antibiotic, was investigated against 492 clinical isolates of gram-positive bacteria, including multiply resistant strains, by an agar-dilution technique. **All streptococci tested were inhibited by the new ketolide at concentrations < or = 0.5 mg/L. HMR 3647 was more potent than erythromycin against staphylococci.** (*Again, evidence of their promise*) For enterococci the new compound yielded an MIC90 of 8 mg/L. Erysipelothrix spp., Pediococcus spp., Leuconostoc spp., Lactobacillus spp., JK diphtheroids and Listeria monocytogenes were also susceptible to the new ketolide.

PMID: 9786468, UI: 99000434

6: J Med Chem 1998 Oct 8;41(21):4080-100

Synthesis and antibacterial activity of ketolides (6-O-methyl-3-oxoerythromycin derivatives): a new class of antibacterials highly potent against macrolide-resistant and -susceptible respiratory pathogens.

Agouridas C, Denis A, Auger JM, Benedetti Y, Bonnefoy A, Bretin F, Chantot JF, Dussarat A, Fromentin C, D'Ambrieres SG, Lachaud S, Laurin P, Le Martret O, Loyau V, Tessot N

Medicinal Chemistry, Core Research Functions, and Anti-Infectives Diseases Group, Hoechst Marion Roussel, 102 route de Noisy, 93235 Romainville Cedex, France.

In the search for new antibiotics active against macrolide-resistant pneumococci and Haemophilus influenzae, we synthesized a new class of 3-oxo-6-O-methylerythromycin derivatives, so-called "ketolides". A keto function

was introduced in position 3 after removal of L-cladinose, a sugar which has long been thought essential. Further modifications of the macrolactone backbone allowed us to obtain three different series of 9-oxime, 11,12-carbamate, and 11, 12-hydrazonocarbamate ketolides. These compounds were found to be very active against penicillin/erythromycin-resistant pneumococci and noninducers of MLSB resistance. The 11,12-substituted ketolide 61 (HMR 3004) demonstrated a potent activity against multiresistant pneumococci associated with a well-balanced activity against all bacteria involved in respiratory infections including H. influenzae, Mycoplasma catarrhalis, group A streptococci, and atypical bacteria. In addition HMR 3004 displayed high therapeutic activity in animals infected by all major strains, irrespective of their resistance phenotype.

PMID: 9767644, UI: 98440464

1: Antimicrob Agents Chemother **2000 Jul**;44(7):1894-9

Antipneumococcal activity of ABT-773 compared to those of 10 other agents.

Davies TA, Ednie LM, Hoellman DM, Pankuch GA, Jacobs MR, Appelbaum PC

Department of Pathology, Hershey Medical Center, Hershey, Pennsylvania 17033, USA.
(*Good interview candidates but might be working with Abbott*)
[Medline record in process]

MICs, time-kills, and postantibiotic effects (PAEs) of ABT-773 (a new ketolide) and 10 other agents were determined against 226 pneumococci. Against 78 ermB- and 44 mefE-containing strains, ABT-773 MICs at which 50% of the isolates tested were inhibited (MIC(50)s) and MIC(90)s were 0.016 to 0.03 and 0.125 &mgr;g/ml, respectively. Clindamycin was active only against macrolide-resistant strains containing mefE (MIC(50), 0.06 &mgr;g/ml; MIC(90), 0.125 &mgr;g/ml). Activities of pristinamycin (MIC(90), 0.5 &mgr;g/ml) and vancomycin (MIC(90), 0.25 &mgr;g/ml) were unaffected by macrolide or penicillin resistance, while beta-lactam MICs rose with those of penicillin G. Against 19 strains with L4 ribosomal protein mutations and two strains with mutations in domain V of 23S rRNA, ABT-773 MICs were 0.03 to 0.25 &mgr;g/ml, while macrolide and azalide MICs were all >/=16.0 &mgr;g/ml. ABT-773 was bactericidal at twice the MIC after 24 h for 8 of 12 strains (including three strains with erythromycin MICs greater than or equal to 64.0 &mgr;g/ml). **Kill kinetics of erythromycin, azithromycin, clarithromycin, and roxithromycin against macrolide-susceptible strains were slower than those of ABT-773.** ABT-773 had longer PAEs than macrolides, azithromycin, clindamycin, or beta-lactams, including against ermB-containing strains. **ABT-773, therefore, shows promising in vitro activity against macrolide-susceptible as well as -resistant pneumococci.** (*Confirms Abbott's statements*)

PMID: 10858350, UI: 20316806

2: Antimicrob Agents Chemother **2000 Jun**;44(6):1562-7

***Studies of the novel ketolide ABT-773: transport, binding to ribosomes, and inhibition of protein synthesis in streptococcus pneumoniae.

Capobianco JO, Cao Z, Shortridge VD, Ma Z, Flamm RK, Zhong P

Infectious Disease Research, Abbott Laboratories, Abbott Park, Illinois 60064, USA.

[Medline record in process]

Macrolide resistance in Streptococcus pneumoniae has been associated with two main mechanisms: target modification by Erm methyltransferases and efflux by macrolide pumps. **The ketolide ABT-773, which has a 3-keto group and no L-cladinose sugar, represents a new class of drugs with in vitro activity against a variety of resistant bacteria. Several approaches were undertaken to understand how ABT-773 was able to defeat resistance mechanisms. We demonstrated tighter ribosome binding of ABT-773 than erythromycin. We also showed that ABT-773 (i) accumulated in macrolide-sensitive S. pneumoniae at a higher rate than erythromycin, (ii) was able to bind with methylated ribosomes, though at lower affinities than with wild-type ribosomes, and (iii) accumulated in S. pneumoniae strains with the efflux-resistant phenotype.**
(*Abbott has done research of the resistance mechanism.*)
PMID: 10817709, UI: 20277881

***3: Antimicrob Agents Chemother 2000 Apr;44(4):1112-3

In vitro activity of ABT 773, a new ketolide antibiotic, against Chlamydia pneumoniae.

Strigl S, Roblin PM, Reznik T, Hammerschlag MR

Division of Infectious Diseases, Department of Pediatrics, State University of New York Health Science Center at Brooklyn, Brooklyn, New York 11203-2098, USA.
(*Possible interview candidates*)
The in vitro activities of ABT 773, telithromycin (HMR 3647), azithromycin, clarithromycin, erythromycin, and levofloxacin were tested against 20 strains of Chlamydia pneumoniae. (*Good, this is a comparative test between Hocest's ketolide and Abbotts*) The MIC at which 90% of the isolates were inhibited and the minimal bactericidal concentration at which 90% of the isolates were killed

by ABT 773 were 0.015 microg/ml (range, 0.008 to 0.015 microg/ml). **ABT 773 was the most active antibiotic tested in this study**. (*This is in vitro, what about comparative animal studies?*)

PMID: 10722526, UI: 20187185

***4: Antimicrob Agents Chemother 2000 Feb;44(2):447-9

In vitro activity of ABT-773, a new ketolide, against recent clinical isolates of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis.

Brueggemann AB, Doern GV, Huynh HK, Wingert EM, Rhomberg PR

Medical Microbiology Division, Department of Pathology, University of Iowa College of Medicine, Iowa City, Iowa 52242, USA.
(*Also a possible interview candidate*)
The in vitro activity of ABT-773 was evaluated against Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis isolates. ABT-773 was the most active antimicrobial tested against S. pneumoniae. **ABT-773 and azithromycin were equivalent in activity against H. influenzae and M. catarrhalis and more active than either clarithromycin or erythromycin**. (*Again, good in vitro results for Abbott*)

PMID: 10639382, UI: 20107001

****
Search Results
Connecting to the search system...

Make sure to print or save this page if you want to keep these results; they may not be available again if you backup!

Full Record 2
DIALOG(R)File 9:Business & Industry(R)
(c) 2000 Resp. DB Svcs. All rts. reserv.

02831133 (THIS IS THE FULLTEXT)
Respiratory Tract Infections: Ketolides Comprise New Family of Antibiotics
(Aventis' antibiotic Telithromycin shows in vitro activity against pathogens that lead to community- acquired respiratory tract infections, according to PROTEKT study)
TB & Outbreaks Week, p N/A
June 13, 2000
DOCUMENT TYPE: Newsletter (United States)
LANGUAGE: English RECORD TYPE: Fulltext

WORD COUNT: 641

ABSTRACT:
Preliminary data reported from PROTEKT (**Prospective Resistant Organism Tracking for the Ketolide Telithromycin**), a global study involving 66 laboratories, has found that telithromycin has demonstrated in vitro activity against pathogens that lead to **community- acquired respiratory tract infections** (**RTIs**). (*This study involves only the Aventis antibiotic, and is sponsored by Aventis)*
Telithromycin is part of new family of antibiotics known as ketolides, being explored as RTIs grow increasingly resistant to commonly used antibiotics. **Globally, RTIs kill more than 50 mil people yearly.** PROTEKT is sponsored by Aventis Pharma. Ketek (telithromycin) was submitted by Aventis Pharmaceuticals to the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products for marketing approval earlier in 2000. Full text further discusses the PROTEKT study.

TEXT:
2000 JUN 13 - (NewsRx.com) -- Bacteria that cause community- acquired respiratory tract infections (RTIs) are growing increasingly resistant to the commonly used antibiotics penicillin and erythromycin.

According to preliminary data reported from PROTEKT (Prospective Resistant Organism Tracking for the Ketolide Telithromycin), a global surveillance study involving 66 laboratories in 20 countries, telithromycin, the first in a new family of antibiotics known as ketolides, demonstrated in vitro activity against specific pathogens - including resistant strains - that lead to these infections. RTIs cause more than 50 million deaths globally each year.

"**The preliminary results from PROTEKT not only underscore the growing problem of bacterial resistance to penicillin, but also reveal alarming rates of bacterial resistance to erythromycin, a widely used macrolide antibiotic,**" concluded lead PROTEKT investigator Dr. David Felmingham, GR Micro Ltd., London, and London School of Hygiene and Tropical Medicine, United Kingdom, who presented the data at the 10th Annual European Congress on Clinical Microbiology, held in Parsippany, New Jersey, during May 2000. "**These data found that telithromycin was active against troublesome bacteria that have grown increasingly resistant to the antibiotics** the world relies upon to treat everyday community-acquired respiratory tract infections."

The PROTEKT study is sponsored by Aventis Pharma. Ketek (telithromycin) was submitted by Aventis Pharmaceuticals to the U.S. Food and Drug

Administration (FDA) and the European Agency for the Evaluation of Medicinal Products for marketing approval earlier in 2000. In clinical studies, the most commonly reported adverse reactions for telithromycin were diarrhea, nausea, dizziness, vomiting, and headache.

In this initial report from the ongoing PROTEKT study, researchers analyzed the susceptibility of six common and atypical community-acquired RTI-causing bacteria to several current treatments including beta-lactams, penicillin derivatives like amoxycillin, and commonly used macrolides such as azithromycin and clarithromycin.

The study is designed to evaluate the in vitro activity of telithromycin, the first in a new family of antibiotics called ketolides, which are characterized by a broad microbiological spectrum, novel mechanism of action, and favorable resistance profile. Telithromycin rapidly kills bacteria by inhibiting protein synthesis. Telithromycin binds directly to two sites on bacterial ribosomes, and binds 10 times more tightly to one of the ribosomes than does erythromycin, a macrolide antibiotic.

Internationally, 66 medical centers are currently participating in PROTEKT. To date, 1,056 clinical isolates of Streptococcus pneumoniae, S. pyogenes, Moraxella catarrhalis, Haemophilus influenzae, H. parainfluenzae, and Staphylococcus aureus were collected from patients with RTIs such as community-acquired pneumonia (CAP), acute sinusitis, acute exacerbations of chronic bronchitis (AECB), otitis media, and pharyngitis. Unlike the methodology of previous surveillance programs, PROTEKT isolates were sent to a central laboratory and analyzed using standardized tests specifically focusing on determining minimum inhibitory concentrations (MIC) of telithromycin.

Results of the study targeting S. pneumoniae demonstrated a 39.6% overall resistance to penicillin, with the highest level in South Korea (80.5%). Resistance to erythromycin was 34.9%, rating highest in South Korea and Japan. No isolate required a telithromycin MIC of more than 0.5 mg/L. Levels of beta-lactamase (which appears to neutralize penicillin erythromycin efficacy) production by isolates of H. influenzae were highest in South Korea (58.6%) and was 15.2% overall. H. parainfluenzae isolates demonstrated lower rates of beta-lactamase production (5.7% overall, 22.2% in Canada, the highest rate). In M. catarrhalis isolates, beta-lactamase production was almost complete (96.9%) and reached 100% in Argentina, South Korea, Japan, and Portugal. With the exception of one isolate (0.5%) from South Korea, telithromycin has demonstrated in vitro activity against S. pyogenes, including erythromycin-resistant strains. It has also demonstrated in vitro activity against mecA-isolates of S. aureus.

These PROTEKT data include isolates from Canada, Argentina, South Korea, Japan, Germany, Portugal, Poland, Switzerland, and the United Kingdom. More comprehensive results are anticipated for presentation at the Interscience Conference on Antimicrobial Agents and Chemotherapy in Toronto, Canada, on September 17-20, 2000.

This article was prepared by TB & Outbreaks Week editors from staff and other reports. Copyright 2000, TB & Outbreaks Week via NewsRx.com.

COMPANY NAMES: AVENTIS PHARMACEUTICALS INC (AVENTIS SA); AVENTIS SA
INDUSTRY NAMES: Pharmaceutical
PRODUCT NAMES: Antibiotics and sulfonamides, systemic and systemic antifungals (283415)
CONCEPT TERMS: All product and service information; Product development
GEOGRAPHIC NAMES: World (WOR)

Full Record 4
DIALOG(R)File 9:Business & Industry(R)

02823103 (THIS IS THE FULLTEXT)
First disclosure of Aventis' early-stage R&D pipeline
(Aventis announced the details of its Euro2.4 bil research and development program for 2000)
Marketletter, p N/A
May 29, 2000
DOCUMENT TYPE: Newsletter ISSN: 0951-3175 (United Kingdom)
LANGUAGE: English RECORD TYPE: Fulltext
WORD COUNT: 1545

ABSTRACT:
The pharmaceutical division of Aventis plans to expanding existing product lines and introduce 15 new compounds in the coming 5 years. It is concentrating on new technologies and its capacity to fuse R&D functions that will produce top-flight novel medicines with less development time. Streamlining its product development process resulted in the elimination of many products from development. Over 60 drugs are still under development. The company has allocated Euro2.4 bil for research and development in 2000.

Among the drugs driving future growth are Allegra/Telfast, Lovenox, Taxotere, Amaryl and Arava. The company also expects benefits from Actonel, Lantus, and Ketek. **Ketek is expected to have over $1 bil in sales.** (*So anticipated sales for Abbott over $500 million is not unrealistic*)
The article elaborates on other products under development, some of which have not yet been branded, and offers projected sales.

TEXT:
In its first R&D presentation since the merger of Hoechst and Rhone-Poulenc to create Aventis, (*Since Aventis is the name of the Hoechst/Rhone-Poulenc merger is Ketek just HMR 3647 which is a Hoechst Marion Roussel antibiotic*) the firm's pharmaceutical division has said that it intends to grow the business by launching 15 new compounds over the next five years, as well as by expanding product lines.

The company focused to a great extent on new technologies which, it says, as well as demonstrating its rapid ability to merge R&D functions, will enable it to reduce the drug discovery time while producing high-quality, innovative medicines. This desire to streamline the R&D process has resulted in a number of compounds (including an oral taxoid) being dropped from development following a detailed review, but leaving more than 60 drugs in the Aventis pipeline. Of these, a certain number are classified as priority programs and will receive the lion's share of available funding (2.4 billion euros ($2.15 billion) has been allocated to R&D this year).

Richard Markham, chief executive of Aventis, told the meeting that the company is on track to deliver promised savings and that it intends to improve growth rates by concentrating promotion on strategic brands. The effects of this focus are already starting to bear fruit, noted Mr Markham; while revenues last year principally derived from older (mainly generic) products, sales of newer "strategic" compounds increased 61% (to 32% of total prescription drug turnover) in the first quarter of 2000, compared to the same period last year, and are forecast to rise to 60% of total Aventis Pharma sales by 2004.

Key drivers of growth

Drivers of future growth are the antiallergy drug Allegra/Telfast (fexofenadine), the antithrombotic Lovenox (enoxaparin), the anticancer agent Taxotere (docetaxel), the antidiabetic drug Amaryl (glimepiride) and Arava (leflunomide) for rheumatoid arthritis. The first four products generated sales of 611 million euros in the first quarter of this year and, despite already being in the top-10 product list, all saw significant growth over the like-period 1999. Arava is not yet a top-10 compound, but is experiencing considerable growth, says the firm.

Growth will also benefit from: the recent launch of Actonel (risedronate) for the treatment of postmenopausal osteoporosis, which is being marketed with Procter & Gamble; Lantus (insulin glargine (rDNA origin) injection), a new once-daily recombinant insulin which has just been approved in the USA; **and Ketek (telithromycin), a novel ketolide antibiotic which has recently been filed for approval in the USA and Europe and is expected to generate sales of more than $1 billion.**

Looking further back in the pipeline, Aventis revealed some compounds for the first time and also discussed their potential benefits over currently-marketed products. Among these key compounds are the VLA-4 (very-late antigen-4) inhibitors, which Aventis is developing initially for asthma but which also have application in rheumatology, central nervous system and cardiovascular indications.

While a number of companies are investigating this class of compounds, Aventis says it has a front-running position with both inhaled and oral formulations. In fact, the firm is evaluating three compounds in parallel in order to assist in lead optimization and to reduce product cycle time. The project is currently in Phase I development in asthma and the firm is looking to demonstrate an increase in forced expiratory volume (FEV1) compared to placebo and and increase or similar similar activity to the leading inhaled steroid, Glaxo Wellcome's Flixotide (fluticasone). Aventis' product has potential steroid-sparing effects, which could help its positioning, although Goldman Sachs analysts say that because it is at such an early stage of development, it has not yet assigned any sales forecasts.

Next is Aventis' 1098, a first-in-class ATP-dependent potassium channel blocker for use in the prevention of sudden cardiac death. While current therapies are available for this indication, their Achilles' heel is a prolongation in QT interval, says Aventis. In contrast, 1098, which is being developed in both oral and intravenous formulations, is activated only in ischemia and has no effect on cardiac parameters under non-ischemic conditions.

Trials of 1098, which is currently in Phase IIa development, will focus on determining the lack of QT prolongation effects following acute myocardial infarction and then in congestive heart failure. With a launch scheduled in 2004, GS analysts class this compound as high-risk and are forecasting peak sales of $300 million. However, Aventis sees a large window of opportunity for 1098, with 20%-25% of patients suffering sudden cardiac death following a first myocardial infarction. Another key advantage, notes the firm, is that the compound may be administered at any time after the MI.

Also in the cardiovascular arena, Aventis is developing a dual angiotensin-converting enzyme and neuroendopeptidase inhibitor for the treatment of hypertension and congestive heart failure. There is a medical need for more antihypertensives, says the firm, because currently-available therapies do not lower systolic blood pressure (an equal or more important factor in premature death than dystolic hypertension) unless given in combination.

This compound is likely to come under the spotlight, working as it does in a similar fashion to Bristol-Myers Squibb's much-lauded Vanlev (omapatrilat). B-MS has just withdrawn its New Drug Application for Vanlev following reports of angioedema (Marketletter May 1), but Aventis said that its molecule has a significantly improved safety profile. Despite this, Aventis intends to study 100240, as it is known, in the most vulnerable population (Afro-Americans with a history of asthma) to ensure that its safety in terms of angioedema and cough is less than (or at least equal to) the incidence seen with ACE inhibitor use. A launch is forecast for 2005, but again the compound is at too early a development stage (Phase I) to predict sales, says GS.

Strong cardiovascular portfolio

Another drug looking for a 2005 launch is Aventis' guanylate cyclase activator (code-named 1766) for use in chronic angina, especially in patients ineligible for bypass surgery or following bypass surgery, and which also has potential in congestive heart failure. The company appears to be positioning 1766 as a safer alternative to nitroglycerin, to which patients often develop tolerance, with an improved dosing regimen of once- or twice-daily versus three to four times a day. Currently in Phase I, Aventis comments that key success factors for this drug will be its efficacy in nitrate-insensitive patients, no cross-tolerance to nitrates and inhibition of platelet aggregation.

Further back in the launch schedule (at 2006) is fibroblast growth factor, a gene therapy product currently being evaluated in Phase I to prevent the need for amputation in severe cases of peripheral artery disease. With no pharmacological treatment available, and 150,000 people requiring amputations every year in the USA alone, the market is potentially large. However, GS notes that although "early indications of data obtained are encouraging....the product is extremely high-risk and early-stage so we have not yet ascribed any sales expectations to it."

Moving on, Aventis is entering another highly competitive field with the development of a once-daily selective estrogen receptor modulator, dubbed 3339, which is currently in Phase IIa clinical trials for use in the

CONFIDENTIAL
JH 002224

prevention and treatment of postmenopausal osteoporosis. The reasons for investigating this compound could be questioned as Eli Lilly's SERM Evista (raloxifene) has been on the market for some time but has failed to take off as expected. Aventis says that 3339 has important advantages over raloxifene in that the latter is a non-steroid-like molecule which is associated with hot flashes in the postmenopausal period as well as intermittent bleeding. In contrast, Aventis' compound is steroid-like and therefore has a mechanism of action that more closely resembles a naturally-occurring molecule, it says.

Aventis hopes to show other benefits over raloxifene in addition to better prevention of menopausal symptoms, including no effect on the breast and uterus and a greater reduction of plasma low-density lipoprotein cholesterol. A launch is unlikely ahead of 2005, says GS, which has forecast peak sales of $350 million.

Another area of focus is rheumatoid arthritis, for which Aventis is investigating an interleukin-1 beta converting enzyme (3480/VX-470) in partnership with Vertex Pharmaceuticals. In Phase IIa clinical studies, the firm hopes to show that this novel anti-inflammatory agent significantly reduces RA symptoms over a three-month period, with no associated increase in opportunistic infections (IL-1 is an important pro-inflammatory cytokine in the host-defense mechanism). A launch of the compound, which has many more potential applications, is slated for 2005 and GS is expecting peak sales in the RA indication of $300 million.

In cancer, Aventis is focusing on flavopiridol (code-named 1275), which has a number of mechanisms of action, including: inhibition of cyclin-dependent kinase; inhibition of tumor blood vessel formation; and induction of caspase-3 activation and cell death. This multiple activity means that flavopiridol cannot be readily bypassed by tumor cells. Other advantages of this first-in-class molecule is that it works independently of prior treatment history and has no overlapping toxicity with commonly-used anticancer agents. Currently in dose-escalating Phase IIa clinical trials, flavopiridol has already shown promise in patients with chronic lymphocytic leukemia (one of the indications Aventis is focusing on), with shrinkage in lymph node size observed and no dose-related toxicity seen. GS believes flavopiridol will be positioned as a combination therapy and has peak sales potential of $350 million following a 2003 launch.

While the eight early-stage products highlighted at the meeting are certainly innovative, GS notes that they are therefore more risky. "The presence of some 'me-too' products, while adding less value in terms of therapeutic advance, might give the pipeline a less risky feel to it," the analysts conclude.

COMPANY NAMES: AVENTIS SA
INDUSTRY NAMES: Pharmaceutical
PRODUCT NAMES: Pharmaceutical preparations (283400)
CONCEPT TERMS: All company; All market information; All product and service information; Corporate strategy; Product development; R&D expenditures; Sales
GEOGRAPHIC NAMES: European Union (EUCX); France (FRA); Western Europe (WEEX)

Charges for the current search: $10.00
_ 2000 Telebase, a division of Office.com Inc.

KLOTZ DEPOSITION EXHIBIT 22

D'S EXHIBIT 554

Klotz
EXHIBIT NO. 22
5-16-07
MICHELLE KEEGAN

From: Lynn C. Klotz [LynnKlotz@compuserve.com]
Sent: Tuesday, July 04, 2000 12:30 PM
To: Blewitt, Stephen
Subject: ketolide research summary

Steve,

Here is the summary research on ketolide antibiotics. This might be the most promising of Abbott's single drugs in the package. It may even achieve the greater than $1 billion market share they project, since Adventis publically projects $1 billion for its ketolide, Ketek, just on the market. Abbott's is not far behind and may have superior properties.

I will complete the summary research writeups on the trip, and send them to you when I return shortly after July 10.

As far as a final report, I will make sure you have all the information verbally first. I am planning one page for each basket item which will summarize the most salient facts. The interviews and slightly polished research summaries will be in Appendices.

-Lynn

Abbott's Ketolide Antibiotic (ABT-773)

file: abbott-ketolide

Potential interviewee's for ABT-773

Stuart Levy (Professor Microbiology Tuft's University School of Medicine, Tel: 617-636-6764, e-mail: stuart.levy@tufts.edu) is a leading authority on antibiotic resistance. If he views ketolides as particularly promising we may not need to interview anyone else.

Malathum K, Coque TM, Singh KV, Murray BE
(*Good interview candidates*)
Center for the Study of Emerging and Re-Emerging Pathogens, University of Texas Medical School, Houston 77030, USA.

Schulin T, Wennersten CB, Moellering RC Jr, Eliopoulos GM
Department of Medicine, Beth Israel Deaconess Medical Center, and Harvard Medical School, Boston, MA 02115, USA.
(*Excellent interview candidates, because of local connection. Does Andy Onderdonk know these researchers*)

Strigl S, Roblin PM, Reznik T, Hammerschlag MR
Division of Infectious Diseases, Department of Pediatrics, State University of New York Health Science Center at Brooklyn, Brooklyn, New York 11203-2098, USA.
(*Possible interview candidates*)

Questions for antibiotic resistance experts on ketolide antibiotics

What new classes of antibiotics show promise against resistant gram-positives?

Of the following new classes, which are the most promising: Quinolones, polyketides, macrolides, ketolides, others? Why?

On average, what percentage of gram-positive infections are resistant to antibiotics? How fast is resistance growing?

Which of the large drug companies do you see as leaders in the development of new antibiotics?

The antibiotic market is highly fragmented. In business terms, there are many antibiotics each with small market share. What would be the properties of a new antibiotic that would make it widely used? Of the development stage antibiotics, do you see one or more that should find wide usage, and thus large market share?

Are there any other approaches to protection against infections that will significantly compete

with antibiotics? Vaccines? Vaccines in edible plants? Others?

Are there any other approaches to antribiotic resistance, besides new antibiotics, that seem promising?

Is there a key question that I did not ask? What is it, and how would you answer it?

Questions for Abbott on ABT-773 and competition

HMR 3647 is a Hoechst Marion Roussel antibiotic. It appears in more than one recent paper as especially promising. In view of the fact that Aventis is the name of the Hoechst/Rhone-Poulenc merger, is Ketek just the new name for HMR 3647?

Is ABT-773 also more effective against strains susceptible to other antibiotics?

What other new classes of antibiotics show promise against resistant gram-positives?

On average, what percentage of gram-positive infections are resistant to antibiotics? How fast is resistance growing?

In one literature report of a comparative test between Hocest's ketolide (HMR 3647) and ABT-773, ABT-773 was found to be more active. Are there other ketolides for which you have comparisons?

How did you arrive at future sales of over $1.3 billion?

Example articles

2: Antimicrob Agents Chemother 2000 Jun;44(6):1562-7
Studies of the novel ketolide ABT-773: transport, binding to ribosomes, and inhibition of protein synthesis in streptococcus pneumoniae.
Capobianco JO, Cao Z, Shortridge VD, Ma Z, Flamm RK, Zhong P
Infectious Disease Research, Abbott Laboratories, Abbott Park, Illinois 60064, USA.
[Medline record in process]
Macrolide resistance in Streptococcus pneumoniae has been associated with two main mechanisms: target modification by Erm methyltransferases and efflux by macrolide pumps. The ketolide ABT-773, which has a 3-keto group and no L-cladinose sugar, represents a new class of drugs with in vitro activity against a variety of resistant bacteria. Several approaches were undertaken to understand how ABT-773 was able to defeat resistance mechanisms. We demonstrated tighter ribosome binding of ABT-773 than erythromycin. We also showed that ABT-773 (i) accumulated in macrolide-sensitive S. pneumoniae at a higher rate than erythromycin, (ii) was able to bind with methylated ribosomes, though at lower affinities than with wild-type ribosomes, and (iii) accumulated in S. pneumoniae strains with the

efflux-resistant phenotype. (*Abbott has done research on the resistance mechanism.*)
PMID: 10817709, UI: 20277881

3: Antimicrob Agents Chemother 2000 Apr;44(4):1112-3
In vitro activity of ABT 773, a new ketolide antibiotic, against Chlamydia pneumoniae.
Strigl S, Roblin PM, Reznik T, Hammerschlag MR
Division of Infectious Diseases, Department of Pediatrics, State University of New York Health Science Center at Brooklyn, Brooklyn, New York 11203-2098, USA.
(*Possible interview candidates*)
The in vitro activities of ABT 773, telithromycin (HMR 3647), azithromycin, clarithromycin, erythromycin, and levofloxacin were tested against 20 strains of Chlamydia pneumoniae. (*Good, this is a comparative test between Hocest's ketolide and Abbotts*) The MIC at which 90% of the isolates were inhibited and the minimal bactericidal concentration at which 90% of the isolates were killed by ABT 773 were 0.015 microg/ml (range, 0.008 to 0.015 microg/ml). ABT 773 was the most active antibiotic tested in this study. (*This is in vitro, what about comparative animal studies?*)
PMID: 10722526, UI: 20187185

4: Antimicrob Agents Chemother 2000 Feb;44(2):447-9
In vitro activity of ABT-773, a new ketolide, against recent clinical isolates of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis.
Brueggemann AB, Doern GV, Huynh HK, Wingert EM, Rhomberg PR
Medical Microbiology Division, Department of Pathology, University of Iowa College of Medicine, Iowa City, Iowa 52242, USA.
(*Also a possible interview candidate*)
The in vitro activity of ABT-773 was evaluated against Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis isolates. ABT-773 was the most active antimicrobial tested against S. pneumoniae. ABT-773 and azithromycin were equivalent in activity against H. influenzae and M. catarrhalis and more active than either clarithromycin or erythromycin. (*Again, good in vitro results for Abbott*)
PMID: 10639382, UI: 20107001

02831133 (THIS IS THE FULLTEXT)
Respiratory Tract Infections: Ketolides Comprise New Family of Antibiotics (Aventis' antibiotic Telithromycin shows in vitro activity against pathogens that lead to community- acquired respiratory tract infections, according to PROTEKT study) TB & Outbreaks Week, p N/A June 13, 2000
DOCUMENT TYPE: Newsletter (United States)
LANGUAGE: English RECORD TYPE: Fulltext
WORD COUNT: 641
ABSTRACT:
Preliminary data reported from PROTEKT (Prospective Resistant Organism Tracking for the Ketolide Telithromycin), a global study involving 66 laboratories, has found that telithromycin

has demonstrated in vitro activity against pathogens that lead to community- acquired respiratory tract infections (RTIs) (*This study involves only the Aventis antibiotic, and is sponsored by Aventis)* Telithromycin is part of new family of antibiotics known as ketolides, being explored as RTIs grow increasingly resistant to commonly used antibiotics. Globally, RTIs kill more than 50 mil people yearly. PROTEKT is sponsored by Aventis Pharma. Ketek (telithromycin) was submitted by Aventis Pharmaceuticals to the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products for marketing approval earlier in 2000. Full text further discusses the PROTEKT study.

KLOTZ DEPOSITION EXHIBIT 25

D'S EXHIBIT 810

Q.

Moxifloxacin

Ketolide Macrolides Glycyclines ~~Abbott's Ketolide~~ Antibiotic (ABT-773) Linezolid ~~Quinolones~~

file: abbott-ketolide

IV half life 5-7h 12-15? ~~Toxicity~~

dosing BID ONCE

G+ G−

Potential interviewee's for ABT-773

Stuart Levy (Professor Microbiology Tuft's University School of Medicine, Tel: 617-636-6764, e-mail: stuart.levy@tufts.edu) is a leading authority on antibiotic resistance. If he views ketolides as particularly promising we may not need to interview anyone else.

S pneumoniae
h. influenza

Malathum K, Coque TM, Singh KV, Murray BE
(Good interview candidates)
Center for the Study of Emerging and Re-Emerging Pathogens, University of Texas Medical School, Houston 77030, USA.

Schulin T, Wennersten CB, Moellering RC Jr, Eliopoulos GM
Department of Medicine, Beth Israel Deaconess Medical Center, and Harvard Medical School, Boston, MA 02115, USA.
(Excellent interview candidates, because of local connection. Does Andy Onderdonk know these researchers)

Strigl S, Roblin PM, Reznik T, Hammerschlag MR
Division of Infectious Diseases, Department of Pediatrics, State University of New York Health Science Center at Brooklyn, Brooklyn, New York 11203-2098, USA.
(Possible interview candidates)

Dr. Robert C. Moellering, Jr. Beth Israel Deaconess Medical Center

Questions for antibiotic resistance experts on ketolide antibiotics

Daptomycin

What new classes of antibiotics show promise against resistant gram-positives? (G+)

Oxazolidinones
Linezolid

Of the following new classes, which are the most promising: Quinolones, polyketides, macrolides, ketolides, others? Why? Glycylcylines

On average, what percentage of gram-positive infections are resistant to antibiotics? How fast is resistance growing?

Which of the large drug companies do you see as leaders in the development of new antibiotics?

The antibiotic market is highly fragmented. In business terms, there are many antibiotics each with small market share. What would be the properties of a new antibiotic that would make it widely used? Of the development stage antibiotics, do you see one or more that should find wide usage, and thus large market share?

Are there any other approaches to protection against infections that will significantly compete

are some targeted to "severe" infection

[illegible] 1 [illegible] to restrict ~~too~~ community [illegible]

with antibiotics? Vaccines? Vaccines in edible plants? Others?

Are there any other approaches to antribiotic resistance, besides new antibiotics, that seem promising? What effect will vaccines, old therapeutics have on market

Is there a key question that I did not ask? What is it, and how would you answer it?

Questions for Abbott on ABT-773 and competition

HMR 3647 is a Hoechst Marion Roussel antibiotic. It appears in more than one recent paper as especially promising. In view of the fact that Aventis is the name of the Hoechst/Rhone-Poulenc merger, is Ketek just the new name for HMR 3647? yes.

Is ABT-773 also more effective against strains susceptible to other antibiotics?

What other new classes of antibiotics show promise against resistant gram-positives?

On average, what percentage of gram-positive infections are resistant to antibiotics? How fast is resistance growing?

In one literature report of a comparative test between Hocest's ketolide (HMR 3647) and ABT-773, ABT-773 was found to be more active. Are there other ketolides for which you have comparisons?

How did you arrive at future sales of over $1.3 billion?

Example articles

2: Antimicrob Agents Chemother 2000 Jun;44(6):1562-7
Studies of the novel ketolide ABT-773: transport, binding to ribosomes, and inhibition of protein synthesis in streptococcus pneumoniae.
Capobianco JO, Cao Z, Shortridge VD, Ma Z, Flamm RK, Zhong P
Infectious Disease Research, Abbott Laboratories, Abbott Park, Illinois 60064, USA.
[Medline record in process]
Macrolide resistance in Streptococcus pneumoniae has been associated with two main mechanisms: target modification by Erm methyltransferases and efflux by macrolide pumps. The ketolide ABT-773, which has a 3-keto group and no L-cladinose sugar, represents a new class of drugs with in vitro activity against a variety of resistant bacteria. Several approaches were undertaken to understand how ABT-773 was able to defeat resistance mechanisms. We demonstrated tighter ribosome binding of ABT-773 than erythromycin. We also showed that ABT-773 (i) accumulated in macrolide-sensitive S. pneumoniae at a higher rate than erythromycin, (ii) was able to bind with methylated ribosomes, though at lower affinities than with wild-type ribosomes, and (iii) accumulated in S. pneumoniae strains with the

efflux-resistant phenotype. (*Abbott has done research on the resistance mechanism.*)
PMID: 10817709, UI: 20277881

3: Antimicrob Agents Chemother 2000 Apr;44(4):1112-3
In vitro activity of ABT 773, a new ketolide antibiotic, against Chlamydia pneumoniae.
Strigl S, Roblin PM, Reznik T, Hammerschlag MR
Division of Infectious Diseases, Department of Pediatrics, State University of
New York Health Science Center at Brooklyn, Brooklyn, New York 11203-2098, USA.
(*Possible interview candidates*)
The in vitro activities of ABT 773, telithromycin (HMR 3647), azithromycin, clarithromycin, erythromycin, and levofloxacin were tested against 20 strains of Chlamydia pneumoniae. (*Good, this is a comparative test between Hocest's ketolide and Abbotts*) The MIC at which 90% of the isolates were inhibited and the minimal bactericidal concentration at which 90% of the isolates were killed by ABT 773 were 0.015 microg/ml (range, 0.008 to 0.015 microg/ml). ABT 773 was the most active antibiotic tested in this study. (*This is in vitro, what about comparative animal studies?*)
PMID: 10722526, UI: 20187185

4: Antimicrob Agents Chemother 2000 Feb;44(2):447-9
In vitro activity of ABT-773, a new ketolide, against recent clinical isolates of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis.
Brueggemann AB, Doern GV, Huynh HK, Wingert EM, Rhomberg PR
Medical Microbiology Division, Department of Pathology, University of Iowa
College of Medicine, Iowa City, Iowa 52242, USA.
(*Also a possible interview candidate*)
The in vitro activity of ABT-773 was evaluated against Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis isolates. ABT-773 was the most active antimicrobial tested against S. pneumoniae. ABT-773 and azithromycin were equivalent in activity against H. influenzae and M. catarrhalis and more active than either clarithromycin or erythromycin. (*Again, good in vitro results for Abbott*)
PMID: 10639382, UI: 20107001

02831133 (THIS IS THE FULLTEXT)
Respiratory Tract Infections: Ketolides Comprise New Family of Antibiotics (Aventis' antibiotic Telithromycin shows in vitro activity against pathogens that lead to community- acquired respiratory tract infections, according to PROTEKT study) TB & Outbreaks Week, p N/A June 13, 2000
DOCUMENT TYPE: Newsletter (United States)
LANGUAGE: English RECORD TYPE: Fulltext
WORD COUNT: 641
ABSTRACT:
Preliminary data reported from PROTEKT (Prospective Resistant Organism Tracking for the Ketolide Telithromycin), a global study involving 66 laboratories, has found that telithromycin

has demonstrated in vitro activity against pathogens that lead to community- acquired respiratory tract infections (RTIs) (*This study involves only the Aventis antibiotic, and is sponsored by Aventis)* Telithromycin is part of new family of antibiotics known as ketolides, being explored as RTIs grow increasingly resistant to commonly used antibiotics. Globally, RTIs kill more than 50 mil people yearly. PROTEKT is sponsored by Aventis Pharma. Ketek (telithromycin) was submitted by Aventis Pharmaceuticals to the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products for marketing approval earlier in 2000. Full text further discusses the PROTEKT study.

KLOTZ DEPOSITION EXHIBIT 26

D'S EXHIBIT 511

Klotz
EXHIBIT NO. 26
5-16-07
MICHELLE KEEGAN

Pertinent Information on Interview Candidates

file: interviews

Cytostatic agents in general. Conduct one interview on the general cytostatic approach. Do not interview the experts on the specific cytostatic basket drugs.

Primary interview candidate:

Carol Dahl, National Cancer Institute (NCI)
Title:
Contact information
Tel:
Fax:
e-mail:
Address:

Alternate candidates:

Lance Liotta, Laboratory of Pathology, NCI.
Title:
Contact information
Tel:
Fax:
e-mail:
Address:

L. Rosen, University of California Los Angeles School of Medicine, Los Angeles, California 10945, USA. LSROSEN@mednet.ucla.edu.
Title:
Contact information
Tel:
Fax:
e-mail:
Address:

Questions for experts in cytostatic therapies

1. Do you see cytostatic therapies being used only on advanced disease? On all disease? Mainly in combination with traditional cytotoxic therapies or as monotherapies? Will cytostatic therapies play a role as adjuncts to surgery and radiation therapy as well?

2. My understanding is that the overall mortality due to metastatic cancer has not been reduced meaningfully in spite of intensive research, does this represent a big opportunity

for cytostatic therapies? How likely is it, in your opinion, that cytostatic therapies will provide big improvements in treatment of metastatic cancers?

3. There are many approaches to cytostatic therapy, such as matrix metalloproteinase inhibitors, farnesyltransferase inhibitors, and tyrosine kinase inhibitors, serine protease inhibitors (e.g., urokinase inhibitors), endothelin ET-1 antagonists (bind to ETA receptors). Did I miss anything in this list(e.g., other approaches to angiogenesis inhibition)? Is there one approach that seems most promising? Least promising? How would you rank them? Is it too early to tell? Which are the most promising candidates within each approach?

4. One literature review indicated that approximately thirty cytostatic agents are in clinical trials to inhibit angiogenesis alone, and another fifty agents are in preclinical testing. Cytostatic drug development is a crowded field. Which of the large drug companies do you perceive as leaders in this area?

5. Matrix metalloproteinase inhibitors seems to be an especially competitive area and have been under development for a long time. Could a first-on-the-market effective matrix metalloproteinase inhibitor (or any cytostatic agent for that matter) kill the opportunities for cytostatic drugs aimed at the other targets?

6. What is known about cost-effectiveness of cytostatic agents? My concern stems from three observations:
   a. They will be administered chronically (daily), which could be expensive;
   b. in one instance (Marimastat), the drug slowed progression but did not prolong life and has painful joint side-effects, so there are no life-years-save and perhaps no quality-life-years-savedd
   c. one literature pharmacoeconomic study indicated that cytostatic treatment with interferon-alpha for multiple myeloma was not cost effective when quality-life-years was used as a measure, because of the drugs toxicity.

7. Since cytostatic therapies don't target killing of tumor cells, the use of time to progression (TTP) of disease seems to be the necessary clinical trials measure? What are the problems with this measure? Do you think the difficulty of measuring TTP will prolong clinical trails or cause some drugs to fail to get approval? How serious an issue is this?

8. The cancer drug field is traditionally highly fragmented. There are many drugs, so the use of any particular drug is limited. In business terms, this means that sales for an average drug is small, less than $100-$200 million. Yet there are some drugs that do sell over $500 million. Do you have any feel whether there will be cytostatic drugs that will sell above $500 million, or do you expect their use and therefore sales to be limited?

9. Is there an important issue we haven't discussed or important question I haven't asked? What is it and what is your opinion?

CONFIDENTIAL
JH 002181

Articles which the candidates have written as reference for interviews:

Cancer Res 1995 May 1;55(9):1856-62
Molecular insights into cancer invasion: strategies for prevention and intervention.
Kohn EC, **Liotta LA**, Laboratory of Pathology, National Cancer Institute, NIH, Bethesda, Maryland 28092, USA.
(*Liotta is a highly regarded cancer researcher. We should interview him or someone from his lab. Get suggestions on whom to interview from Carol Dahl. This particular article, however, is old.*)
The diagnosis and treatment of solid tumors usually begins at a late stage when most patients already have occult or overt metastasis. Many years of cancer progression precede diagnosis of most solid tumors. Novel noncytotoxic therapeutics may be specially suited for administration during this interval. An important window of intervention can be defined as the period during which transition from a hyperproliferative state to acquisition of the capacity for invasion and metastasis occurs. Investigation of the molecular basis of invasion is uncovering strategies for delaying progression of preinvasive carcinoma and treatment of primary tumors and established metastasis. Although tumor cell invasion might not be rate limiting for the growth of metastasis, anti-invasive agents can block tumor angiogenesis and thereby indirectly block metastasis growth. Two classes of molecular anti-invasion targets exist: (a) cell surface and extracellular proteins, which mediate sensing, adhesion, and proteolysis; and (b) signal transduction pathways, which regulate invasion, angiogenesis, and proliferation. Both categories of targets yield treatment approaches that are now being tested in the clinic. Metalloproteinase inhibitors, such as BB94, are based on the recognition that metalloproteinases play a necessary role in invasion and angiogenesis. (*Today–five years later–what is the status of BB94?*) The orally active signal transduction inhibitor carboxyamidotriazole modulates non-voltage-gated calcium influx-regulated signal pathways and reversibly inhibits tumor invasion, growth, and angiogenesis. Blockade of invasion, angiogenesis, or cellular signal pathways is likely to generate a cytostatic, rather than a cytotoxic effect. Cytostatic therapy constitutes an alternative paradigm for clinical translation that may complement conventional cytotoxic therapy. For patients with newly diagnosed solid tumors, long-term cytostatic therapy could potentially create a state of metastasis dormancy or delay the time to overt relapse following cytotoxic agent-induced remission. Clinical toxicity and pharmacology using oral cytostatic agents in phase I trials and in adjuvant settings will provide an important foundation for the translation of this approach to the preinvasive carcinoma period.

Oncologist 2000;5 Suppl 1:20-7
Antiangiogenic strategies and agents in clinical trials.
Rosen L
University of California Los Angeles School of Medicine, Los Angeles, California 10945, USA. LSROSEN@mednet.ucla.edu
The understanding that the growth of tumors depends on the acquisition of a blood supply has led to the development of new therapies for cancer and other angiogenic diseases based on inhibition of neovascularization. This review examines the role of angiogenesis in cancer progression and describes various strategies for interfering with this process. The developmental status of

angiogenesis inhibitors in human clinical trials is presented, including their proposed mechanisms of action. (*This statement indicates this person should be interviewed, especially since this is a brand-new paper, but e-mail him to try to get a copy of the paper first.*) Standard chemotherapeutic agents and angiogenesis inhibitors are compared, noting that different end points might need to be considered in clinical trials and that drug resistance may be less of a problem with antiangiogenic therapy than with conventional chemotherapy regimens. The suggestion is made that cytotoxic chemotherapy and angiogenesis inhibitors used in combination may produce complementary therapeutic benefits in the treatment of cancer.

<u>**ABT-627. Endothelin ET-1 inhibitor**</u> (Interview one candidate)

Primary interview candidate:

Ripple GH, Wilding G (wrote a recent review: Drug Development in Prostate Cancer.)
Title:
Contact information
Tel:
Fax:
e-mail:
Address:

Alternates:

Hsu JY, Pfahl M, Sidney Kimmel Cancer Center, San Diego, California 92121, USA.
Title:
Contact information
Tel:
Fax:
e-mail:
Address:

Kroodsma JM, Rabelink AJ, Academisch Ziekenhuis, afd. Nefrologie, Utrecht.
Title:
Contact information
Tel:
Fax:
e-mail:
Address:

Questions for experts in therapies for late stage prostate cancer

<u>Questions for ABT-627 interviewees</u>

Note to orient me on mechanism: The endothelins (ET-1, ET-2 and ET-3 are a family of 21 amino acid peptides that bind. Endothelin's are potent vasoconstictors that act through binding to the Eta receptor. Drugs that bind to the Eta receptor (e.g., ABT-627) inhibit ET-1 from binding to the receptor (termed ET-1 antagonists). Such drugs may retard cancer growth and reduce pain. Abbott claims that the role of endothelins in the manifestation of metastatic cancer is not yet defined.

10. How do vasoconstrictors retard cancer? I presume vasoconstriction means reduced blood flow to a tumor, so why would you want an ET-1 antagonist? Or is it just that any drug

that binds to the Eta receptor would retard cancer?

11. What is the evidence that blocking endothelin receptors will have clinical value in the treatment of metastasized prostate cancer?

12. Is blocking the ETa receptor with an endothelin-1 (ET-1) antagonist the best strategy?

13. The literature mentions several drugs mostly by alpha-numeric name: BQ-123, A127722, ABT-627, Novantrone (already on market), and retinoids (which reduces ET-1 transcription). Do you have an opinion on the promise and issues with these drugs? Which companies are developing these drugs?

14. The Japanese company Yamanouchi supposedly has a drug in clinical trials? Name? Targets? Promise? Clinical trial status?

15. What other targets for slowing metastasis of prostate cancer are promising? For example, would an inhibitor targeting the ET-1 converting enzyme phosphoramidon be a good target? Other targets in the pathway to metastasis?

16. One literature study indicated that a number of factors: 1beta (IL-1beta), tumour necrosis factor alpha (TNF-alpha) and transforming growth factor beta (TGF-beta) stimulated ET-1 and big ET-1 secretion, is there merit to targeting any of these to slow metastasis?

17. Do you think a drug that successfully slows metastasis of prostate cancer would be widely used? For which patients would such a drug be prescribed? What percentage of prostate cancer patients fall into that category? What number of quality-life-years might such a drug provide?

18. Drugs that slow metastasis, angiogenesis, etc. that don't usually kill the cancer cells have been dubbed cytostatic therapy? In general, how promising is cytostatic therapy? Has its value been proven anywhere?

19. There are many approaches to cytostatic therapy, such as matrix metalloproteinase inhibitors, farnesyltransferase inhibitors, and tyrosine kinase inhibitors, serine protease inhibitors (e.g., urokinase inhibitors), endothelin ET-1 antagonists (bind to ETA receptors). Did I miss anything in this list(e.g., other approaches to angiogenesis inhibition)? Is there one approach that seems most promising? Least promising? How would you rank them? Is it too early to tell? Which are the most promising candidates within each approach?

20. One literature review indicated that approximately thirty cytostatic agents are in clinical trials to inhibit angiogenesis alone, and another fifty agents are in preclinical testing. Cytostatic drug development is a crowded field. Which of the large drug companies do you perceive as leaders in this area?

21. Is there an important issue we haven't discussed or important question I haven't asked? What is it and what is your opinion?

Articles which the candidates have written as reference for interviews:

6: Semin Oncol 1999 Apr;26(2):217-26
Drug development in prostate cancer.
Ripple GH, Wilding G
Department of Medicine, University of Wisconsin Comprehensive Cancer Center, Madison, USA.
Despite strategies aimed at early detection and treatment, prostate cancer remains a leading cause of morbidity and mortality among males. Current therapies have limited impact on the natural history of metastatic hormone-refractory prostate cancer (HRPC). With an improved understanding of tumor biology, including apoptosis, differentiation, cell cycling and signaling, and angiogenesis, many potential new targets for therapy have been unveiled. Modulation of these processes may result in cytotoxic or cytostatic effects. The evaluation of therapies based on manipulation of these targets may not be adequately addressed by current study designs and traditional parameters of efficacy. Examples of agents currently in clinical trials that illustrate some of the challenges presented to clinical investigators include monoterpenes such as perillyl alcohol (POH), vitamin D analogs, flavones such as flavopiridol, and angiogenesis inhibitors. Agents such as these are aimed at unique cellular targets and will require novel approaches to determine their clinical utility. Unfortunately, in the United States, only a small proportion of cancer patients, including prostate cancer patients, are enrolled in clinical trials. We must do better to efficiently assess promising new treatment approaches and improve outcome for our patients.
Publication Types:
Review
Review, tutorial
PMID: 10597732, UI: 20064602

6:Cancer Res 1998 Nov 1;58(21):4817-22
ET-1 expression and growth inhibition of prostate cancer cells: a retinoid target with novel specificity.
Hsu JY, Pfahl M
Sidney Kimmel Cancer Center, San Diego, California 92121, USA.
Endothelin-1 (ET-1) is not only a potent vasoconstrictor but also serves as an important growth stimulator in various cancers, including breast, cervical, pancreatic, and prostate cancer. This suggests that blockage of ET-1 production may suppress tumor growth and possibly metastasis. We observed that certain synthetic retinoids, and all-trans-retinoic acid can repress LNCaP prostate cancer cell growth in vitro. In addition, these retinoid compounds counteracted exogenous ET-1-induced growth stimulation. Retinoid-dependent growth retardation of LNCaP cells coincided with suppression of ET-1 gene expression to a level undetectable by reverse transcription-PCR. (How do *the small-molecule retenoid drugs suppress ET-1 gene expression (affect promotor activity, see below)? Is ABT-627 a retenoid compound which works at the level of transscrition, or is a traditional antagonist binding directly to the Eta receptor? Do retenoids*

CONFIDENTIAL
JH 002186

represent serius competition to ABT-627? Are they in development and by whom?) Contrarily, the androgen-insensitive DU145 cells were refractory to retinoid treatment. To investigate the underlying mechanisms of the cell-specific response to retinoids, we transfected ET-1 promoter constructs containing wild-type or mutated AP-1 or GATA-2 site into prostate cancer cells. Distinct regulations of ET-1 promoter activity were found; in LNCaP cells, both binding sites are essential for optimal promoter activation, whereas in DU145 cells, additional promoter sequences and/or transcriptional factors seem to be involved. Furthermore, several anti-AP-1 selective retinoids failed to repress ET-1 promoter activity and to exhibit a cell growth-inhibitory effect on LNCaP cells, suggesting that different retinoid structural configurations are required for the inhibition of an AP-1 complex versus an AP-1/GATA-2 complex.
PMID: 9809984, UI: 99025856

7:Ned Tijdschr Geneeskd 1997 Sep 20;141(38):1806-10
[Endothelins: possibly a new pharmacological approach in cardiovascular diseases, kidney diseases and oncological disorders].
[Article in Dutch]
Kroodsma JM, Rabelink AJ
Academisch Ziekenhuis, afd. Nefrologie, Utrecht.
Only 10 years ago, the vasoconstricting peptide endothelin was discovered; it is produced by endothelial cells. Different isoforms and receptors of endothelin have been identified. The effects of endothelin-I, the most important isoform, are mainly vasoconstriction and proliferation of cells. (*ET-1 is the most important ET isoform*) In the last few years endothelin receptor antagonists have become available, which can delineate the clinical importance of the endothelin system. Possible indications for endothelin receptor blockers are renal disease (acute and chronic renal failure) and cardiovascular disease (heart failure; restenosis after percutaneous transluminal coronary angioplasty (PTCA); pulmonary hypertension; systemic hypertension). There is also a possible role for endothelin receptor blockers in oncology (prostatic carcinoma). (*This 1997 paper talks about possible roles of Eta blockers in prostate cancer.*) Currently clinical trials are being carried out to determine the efficacy of these compounds for the above-mentioned indications. (*Do these authors know of other clinical trials in progress?*)
Publication Types:
Review
Review, tutorial
PMID: 9545734, UI: 98207344

A-254751. Cytotoxic therapy for late stage cancer (bind to colchicine site of tubulin to prevent microtubule formation. (Interview two candidates because of questions of toxicity)

Primary interview candidates:

Kudelka AP, Hasenburg A, Verschraegen CF, Edwards CL, Meyers CA, Varma D, Freedman RS, Forman A, Conrad CA, Grove W, Grothey A, Kavanagh JJ
University of Texas MD Anderson Cancer Center, Houston 77030-4095, USA.
Title:
Contact information
Tel:
Fax:
e-mail:
Address:

Leoni LM, Hamel E, Genini D, Shih H, Carrera CJ, Cottam HB, Carson DA
Department of Medicine and The Sam and Rose Stein Institute for Research on Aging, University of California San Diego, La Jolla 92093, USA. lleoni@ucsd.edu
(*potential interview candidates*)

Title:
Contact information
Tel:
Fax:
e-mail:
Address:

Questions for experts in microtubulin-destabilizing cytotoxic cancer therapies cancer:

22. There are a number of colchincine-site binding agents in preclinical and in clinical trials. Some that we have identified are: combretastatin-A4 (Oxigene), T138607 and T900607(Tularik), Amphethinlle (ICI), 1069C (Wellcome), trimethylcholinic acid (NIH), A-254751 (Abbott), indanocine, tricyclic pyrones, H-10, curacin A,. Are you familiar with some of these? Do any stand out as especially promising?

23. What is the theorectical reason for targeting the colchicine site?

24. There are also a number of Vinca-alkaloid site ligands in development, which I believe are also antimitotic agents. Do both types block tubulin formation? Are there any perceived advantages/disadvantages to each target?

25. The Parke Davis drug, CI-980, was just abandoned in Phase II clinical trials. Since it was in Phase II, was lack of efficacy reason for abondonment, or the dose-limiting toxicities seen in Phase I? A number of other colchicine-site drugs have also been abandoned in

clinical trials, and I believe none have made it to market? Since all target the colchicine-binding site, could most of the new drugs also suffer the same clinical trial fate. Put another way, what does this say about the prospects for colchicine binding drugs in general?

26. One drug, the antimitotic H10 is described as a bifunctional anticancer drug: antimitotic and also blocks the cellular transport of to inhibit DNA synthesis. Bifunctionality is perhaps an interesting observation, but is it clinically significant?

27. A study by Ajinomoto indicated that some tubulin binding agents also exhibit cystostatic antivascular effects. Also, a UCSD study on indanocine states that it is both a cytostatic and cytotoxic agent. Are the antivascular effects due to tubulin binding of fast-growing vasculature at the tumor site, and so are to be expected with all tubulin binding agents?

28. Is there an important issue we haven't discussed or important question I haven't asked? What is it and what is your opinion?

Articles which the interview candidates have written as reference for interviews:

Anticancer Drugs 1998 Jun;9(5):405-9
Phase II study of i.v. CI-980 in patients with advanced platinum refractory epithelial ovarian carcinoma.
Kudelka AP, Hasenburg A, Verschraegen CF, Edwards CL, Meyers CA, Varma D, Freedman RS, Forman A, Conrad CA, Grove W, Grothey A, Kavanagh JJ
University of Texas MD Anderson Cancer Center, Houston 77030-4095, USA.

CI-980 is a synthetic mitotic inhibitor that binds to tubulin at the colchicine site, inhibiting the polymerization of microtubules and arresting cellular division in metaphase. Myelosuppression and neurotoxicity were dose-limiting in phase I studies. (*CI-980 is the Parke Davis drug just abandoned in Phase II clinical trials. Since it was in Phase II, was lack of efficacy reason for abondonment, or the dose-limiting toxicities seen in Phase I? A number of other colchicine binding drugs have also been abandoned in clinical trials and none have made it to market? Since the mechanism of CI-980 and the other abandoned drugs is the same as the preclinical A-254751, couldn't A-254751 suffer the same fate. Abbott is already anticipating vasoconstriction risk in humans from its studies in dogs. Why does Abbott think it will not suffer the same fate in human trials?*) Sixteen patients with stage III and IV platinum-refractory ovarian cancer received 4.5 mg/m2/day of CI-980 as a continuous i.v. infusion for 72 h, repeated every 3 weeks. Eleven patients had progression and four patients had stable disease. One patient (6%; 95% CI 0-25%) achieved a partial response after 9 months of treatment which lasted for 27 months. The overall median survival was 7 months. Grade 4 granulocytopenia occurred in five patients, with two episodes of neutropenic fever. Neurological toxicity was mild with 12 episodes of transient subclinical recent memory loss documented in four patients by specialized neuropsychological evaluations. One patient each had hallucinations and mild truncal ataxia, and four patients had mild, reversible neurosensory toxicity. One episode of severe hypoxemia and dyspnea occurred in a patient with chronic obstructive pulmonary disease. CI-980 has minimal activity and is

tolerable in a population of heavily pretreated patients with platinum refractory ovarian cancer. (*As this is a Phase II trial, the minimal efficacy here may be the reason for abandonment. What does this say about the prospects for colchicine binding drugs in general?*)
Publication Types:
Clinical trial
Clinical trial, phase ii
PMID: 9660537, UI: 98321974

J Natl Cancer Inst 2000 Feb 2;92(3):217-24
Indanocine, a microtubule-binding indanone and a selective inducer of apoptosis in multidrug-resistant cancer cells.
Leoni LM, Hamel E, Genini D, Shih H, Carrera CJ, Cottam HB, Carson DA
Department of Medicine and The Sam and Rose Stein Institute for Research on Aging, University of California San Diego, La Jolla 92093, USA. lleoni@ucsd.edu
BACKGROUND: Certain antimitotic drugs have antitumor activities that apparently result from interactions with nontubulin components involved in cell growth and/or apoptotic cell death. Indanocine is a synthetic indanone that has been identified by the National Cancer Institute's Developmental Therapeutics Program as having antiproliferative activity. In this study, we characterized the activity of this new antimitotic drug toward malignant cells. METHODS: We tested antiproliferative activity with an MTT [i.e., 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] assay, mitochondrial damage and cell cycle perturbations with flow cytometry, caspase-3 activation with fluorometry, alterations of the cytoskeletal components with immunofluorescence, and antimicrotubule activity with a tubulin polymerization assay. RESULTS/CONCLUSIONS: Indanocine is a cytostatic and cytotoxic indanone that blocks tubulin polymerization but, unlike other antimitotic agents, induces apoptotic cell death in stationary-phase multidrug-resistant cancer cells at concentrations that do not impair the viability of normal nonproliferating cells. Of the seven multidrug-resistant cell lines tested, three (i.e., MCF-7/ADR, MES-SA/DX5, and HL-60/ADR) were more sensitive to growth inhibition by indanocine than were their corresponding parental cells. Confluent multidrug-resistant cells (MCF-7/ADR), but not drug-sensitive cancer cells (MCF-7) or normal peripheral blood lymphocytes, underwent apoptotic cell death 8-24 hours after exposure to indanocine, as measured by sequential changes in mitochondrial membrane potential, caspase activity, and DNA fragmentation. Indanocine interacts with tubulin at the colchicine-binding site, potently inhibits tubulin polymerization in vitro, and disrupts the mitotic apparatus in dividing cells. IMPLICATIONS: The sensitivity of stationary multidrug-resistant cancer cells to indanocine suggests that indanocine and related indanones be considered as lead compounds for the development of chemotherapeutic strategies for drug-resistant malignancies.
Comments:
Comment in: J Natl Cancer Inst 2000 Feb 2;92(3):182-3

ABT-980. Alpha 1a adrenoceptor antagonist for BPH. (Interview one candidate)

Primary interview candidate:

Cooper KL, McKiernan JM, Kaplan SA
Department of Urology, College of Physicians and Surgeons, Columbia University, New York, New York, USA.
Title:
Contact information
Tel:
Fax:
e-mail:
Address:

Alternate candidates:

Beduschi MC, Beduschi R, Oesterling JE
Section of Urology, University of Michigan, Ann Arbor, USA.
(*Good interview candidates*)
Title:
Contact information
Tel:
Fax:
e-mail:
Address:

Lepor H
Department of Urology, New York University Medical Center, New York 10016, USA.
(*possible interview candidate, but may be working with company marketing tamsulosin*)
Title:
Contact information
Tel:
Fax:
e-mail:
Address:

Questions for experts in BPH:

Note to help orient discussion: "The development of alpha-adrenergic blocking agents, [has proceeded] from nonselective alpha-antagonists, to selective alpha1-antagonists, to the more selective alpha1A-antagonists. It is anticipated that more specific agents will optimize the therapeutic effectiveness of alpha-adrenergic blockade in the prostate while reducing the side effects associated with alpha-adrenergic blockade in other areas of the body, such as the vascular system."

29. Recently, efforts have focused on use of alpha1A-urospecific antagonists such as tamsulosin, alfuzosin, and Abbott-980 in an attempt to achieve similar clinical results as doxazosin and terazosin without systemic adverse effects. Are these alpha1A selective drugs expected to be significantly superior to the older drugs? Why? Are all these drugs structurally different and what is the implication regarding toxicity, potency and pharmacokinetics?

30. How significant a difference is there in urinary flow rates between the older drugs terazosin, finasteride, etc. and the new selective drugs like Tamsulosin. If there is not much difference, why is Tamsulosin use increasing so rapidly? Is it because there is a significant difference of adverse effects with the selective alpha1a-adrenoceptor antagonists?

31. One review article states "controversy remains as to whether prostatic smooth muscle contraction is mediated by the alpha1A-adrenoceptor, or by another novel alpha1-adrenoceptor subtype (not corresponding to any of the three known recombinant alpha1-adrenoceptors)." This indicates there could be a better target, as yet undiscovered. What is your view on this?

32. One literature study refers to a patient population that is responsive to alpha1-adrenoceptor antagonists. Does this mean there is a subgroup of patients that don't respond to BPH drugs targeted to alpha1-adrenoceptor? How big is this subgroup?

33. How would you compare the drugs in clinical trials Dutasteride, Xatra (alfuzosin), HP-4, ABT-980, KMD-3213? Which is most promising? Least promising? Why? Am I missing any promising ones.

34. Yamanouchi/Glaxo's Phase III drug duasteride is a 5alpha-reductase inhibitor. What are the advantages/disadvantages of this target versus alpha1A-adrenoceptor targeted drugs? Could one advantage be that there are less enzyme targets than membrane receptor targets, so that an enzyme inhibitor could be used in much lesser concentrations?

35. Is there an important issue we haven't discussed or important question I haven't asked? What is it and what is your opinion?

Articles which the interview candidates have written as reference for interviews:

Drugs 1999 Jan;57(1):9-17
Alpha-adrenoceptor antagonists in the treatment of benign prostatic hyperplasia.
Cooper KL, McKiernan JM, Kaplan SA
Department of Urology, College of Physicians and Surgeons, Columbia University, New York, New York, USA.
(*potential interview candidates*)
Lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH) have a significant impact on the lifestyle of older men. Transurethral resection of the prostate (TURP) is the most

effective surgical therapy for this condition but an increasing number of patients are electing conservative medical therapy. Alpha-Adrenoceptor antagonists and 5alpha-reductase inhibitors are the 2 categories of drug therapy currently available for BPH. *(Yamanouchi/Glaxo's Phase III drug duasteride is a 5-alpha drug. What are the advantages/disadvantages of this target?* Use of alpha-adrenoceptor antagonists in the treatment of BPH is based on their ability to prevent the neural stimulation which induces prostate smooth muscle contraction, producing lower urinary tract symptoms. Several studies have demonstrated that alpha-receptors predominate in the prostatic stroma, capsule and bladder neck. Initial work focused on the use of phenoxybenzamine, a nonspecific alpha-blocker, in the treatment of BPH. While results were promising, significant adverse effects and concern over potential mutagenicity have resulted in a lack of use of this medication for this indication. Subsequent attention was directed towards the short-acting alpha-specific antagonist prazosin. Results conflicted regarding whether an actual sustained improvement in lower urinary tract symptoms could be achieved with this medication, and because of twice daily dosing compliance issues were a drawback. Thus, the mainstay in pharmacological treatment of BPH over the past decade has been 2 once-a-day alpha-specific antagonists, doxazosin and terazosin. Over 75% of all prescriptions written for BPH are for one of these 2 medications. Despite their tremendous success in both decreasing urinary symptoms and increasing urinary flow rates, systemic adverse effects can be bothersome. Recently, efforts have focused on use of alpha1A-urospecific antagonists such as tamsulosin and alfuzosin in an attempt to achieve similar clinical results as doxazosin and terazosin without systemic adverse effects. (*Alfuzosin (Xatral) is Synthelabo's drug in Phase II. What are its advantages, disadvantages with respect to ABT-980?*) Thus far, results are promising, but long term studies must be done to determine whether pharmacological uroselectivity is actually clinically relevant. (What is the meaning of this cautionary note?)
Publication Types:
Review
Review, tutorial
PMID: 9951948, UI: 99135419

9: Urology 1998 Jun;51(6):861-72
Alpha-blockade therapy for benign prostatic hyperplasia: from a nonselective to a more selective alpha1A-adrenergic antagonist.
Beduschi MC, Beduschi R, Oesterling JE
Section of Urology, University of Michigan, Ann Arbor, USA.
(*Good interview candidates*)
Benign prostatic hyperplasia (BPH) is very common in older men, causing symptoms that can markedly impair quality of life. Surgical treatment, typically transurethral resection of the prostate (TURP), is highly effective but can be costly and is associated with the risk for significant morbidity. Medical treatments for BPH are targeted toward reducing bladder outlet obstruction either by androgen blockade to reduce prostatic volume or alpha-adrenergic blockade to relax the smooth muscle tone of the prostate. In recent years, understanding of the sympathetic innervation of the prostate has improved. This has been paralleled by the development of alpha-adrenergic blocking agents, from nonselective alpha-antagonists, to selective alpha1-antagonists, to the more selective alpha1A-antagonists. It is anticipated that more specific agents will optimize the therapeutic effectiveness of alpha-adrenergic blockade in the prostate

while reducing the side effects associated with alpha-adrenergic blockade in other areas of the body, such as the vascular system. This article reviews the evolution of alpha-blockade therapy in management of BPH, focusing on tamsulosin, an agent targeted toward the alpha1A-adrenoceptor that predominates in the prostate. Clinical trials in Europe and the United States have provided evidence that tamsulosin is effective at doses of 0.4 and 0.8 mg/day. At both doses, tamsulosin is associated with significant improvements in the American Urological Association symptom score and the mean and peak urinary flow rates as compared with placebo. This once-daily alpha1A-adrenergic antagonist is well-tolerated, with a minimal potential for the side effects associated with alphas-blocker therapy.

Publication Types:

Review

Review, tutorial

PMID: 9609620, UI: 98270783

<u>ABT-773. Ketolide antibiotic for resistant bacteria</u> (This is technically straight-forward. Only one interview.)

Primary interview candidates:

Stuart Levy (Professor Microbiology Tuft's University School of Medicine, Tel: 617-636-6764, e-mail: stuart.levy@tufts.edu) is a leading authority on antibiotic resistance. If he views ketolides as particularly promising we may not need to interview anyone else.

Schulin T, Wennersten CB, Moellering RC Jr, Eliopoulos GM
Department of Medicine, Beth Israel Deaconess Medical Center, and Harvard Medical School, Boston, MA 02115, USA.
(Excellent interview candidates, because of local connection. Does Andy Onderdonk know these researchers)

Alternate interview candidate:

Malathum K, Coque TM, Singh KV, Murray BE
Center for the Study of Emerging and Re-Emerging Pathogens, University of Texas Medical School, Houston 77030, USA.

Questions for experts on ketolide antibiotics and antibiotic resistance

1. What new classes of antibiotics show promise against resistant gram-positives?

2. Of the following new classes, which are the most promising: Quinolones, polyketides, macrolides, ketolides, others? Why?

3. On average, what percentage of gram-positive infections are resistant to antibiotics? How fast is resistance growing?

4. Which of the large drug companies do you see as leaders in the development of new antibiotics?

5. The antibiotic market is highly fragmented. In business terms, there are many antibiotics each with small market share. What would be the properties of a new antibiotic that would make it widely used? Of the development stage antibiotics, do you see one or more that should find wide usage, and thus large market share?

6. Are there any other approaches to protection against infections that will significantly compete with antibiotics? Vaccines? Vaccines in edible plants? Others?

7. Are there any other approaches to antribiotic resistance, besides new antibiotics, that seem promising?

8. Is there an important issue we haven't discussed or important question I haven't asked? What is it and what is your opinion?

Articles which the interview candidates have written as reference for interviews:

J Antimicrob Chemother 1998 Sep;42(3):297-301
In-vitro activity of the new ketolide antibiotic HMR 3647 against gram-positive bacteria.
Schulin T, Wennersten CB, Moellering RC Jr, Eliopoulos GM
(*excellent interview candidates, because of local connection*)
Department of Medicine, Beth Israel Deaconess Medical Center, and Harvard Medical School, Boston, MA 02115, USA.
(*Does Andy Onderdonk know these researchers*)
The comparative in-vitro activity of HMR 3647, a new ketolide antibiotic, was investigated against 492 clinical isolates of gram-positive bacteria, including multiply resistant strains, by an agar-dilution technique. All streptococci tested were inhibited by the new ketolide at concentrations < or = 0.5 mg/L. HMR 3647 was more potent than erythromycin against staphylococci. (*Again, evidence of their promise*) For enterococci the new compound yielded an MIC90 of 8 mg/L. Erysipelothrix spp., Pediococcus spp., Leuconostoc spp., Lactobacillus spp., JK diphtheroids and Listeria monocytogenes were also susceptible to the new ketolide.
PMID: 9786468, UI: 99000434

Antimicrob Agents Chemother 1999 Apr;43(4):930-6
In vitro activities of two ketolides, HMR 3647 and HMR 3004, against gram-positive bacteria.
Malathum K, Coque TM, Singh KV, Murray BE
(*Good interview candidates*)
Center for the Study of Emerging and Re-Emerging Pathogens, University of Texas Medical School, Houston 77030, USA.
The in vitro activities of two new ketolides, HMR 3647 and HMR 3004, were tested by the agar dilution method against 280 strains of gram-positive bacteria with different antibiotic susceptibility profiles, including Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium, Streptococcus spp. (group A streptococci, group B streptococci, Streptococcus pneumoniae, and alpha-hemolytic streptococci). Seventeen erythromycin-susceptible (Ems), methicillin-susceptible S. aureus strains were found to have HMR 3647 and HMR 3004 MICs 4- to 16-fold lower than those of erythromycin (MIC at which 50% of isolates were inhibited [MIC50] [HMR 3647 and HMR 3004], 0.03 microgram/ml; range, 0.03 to 0.06 microgram/ml; MIC50 [erythromycin], 0.25 microgram/ml; range, 0.25 to 0.5 microgram/ml). All methicillin-resistant S. aureus strains tested were resistant to erythromycin and had HMR 3647 and HMR 3004 MICs of > 64 micrograms/ml. The ketolides were slightly more active against E. faecalis than against E. faecium, and MICs for individual strains varied with erythromycin susceptibility. The MIC50s of HMR 3647 and HMR 3004 against Ems enterococci (MIC < or = 0.5 microgram/ml) and those enterococcal isolates with erythromycin MICs of 1 to 16 micrograms/ml were 0.015 microgram/ml. E. faecalis strains that had erythromycin MICs of 128 to > 512 micrograms/ml showed HMR 3647 MICs in the range of 0.03 to 16 micrograms/ml and HMR 3004 MICs in the range of 0.03 to 64 micrograms/ml. In the group of E. faecium strains for which MICs of erythromycin were > or = 512 micrograms/ml, MICs of both ketolides were in the

range of 1 to 64 micrograms/ml, with almost all isolates showing ketolide MICs of < or = 16 micrograms/ml. The ketolides were also more active than erythromycin against group A streptococci, group B streptococci, S. pneumoniae, rhodococci, leuconostocs, pediococci, lactobacilli, and diphtheroids. Time-kill studies showed bactericidal activity against one strain of S. aureus among the four strains tested. The increased activity of ketolides against gram-positive bacteria suggests that further study of these agents for possible efficacy against infections caused by these bacteria is warranted.
PMID: 10103202, UI: 99216907

ABT-594. Cholinoergic channel agonist for diabetic neuropathic pain. (Two interviews because of questions about efficacy.)

Potential interview candidates:

Belgrade MJ
(*Good interview candidate*)
Fairview Pain Management Center, Fairview-University Medical Center,
Minneapolis, MN 55454, USA. mbelgra1@fairview.org

Miroslav "Misha" Backonja, M.D., Associate Professor of Neurology and Anesthesiology and the Director of the UW Neurology Pain Clinic.
Contact Information
Department of Neurology,
H6/570 University of Wisconsin Hospital
600 Highland Avenue Madison, WI 53792 Tel: 608/263-5448
Fax:608/263-0412
E-mail: backonja@neurology.Wisc.edu

Nelson KA, Park KM, Robinovitz E, Tsigos C, Max MB Pain and Neurosensory Mechanisms Branch, National Institute of Dental Research, National Institutes of Health, Bethesda, MD 20892-1258, USA.
Mail addressed to mm77k@nih.gov will be forwarded to mmax@dir.nidcr.nih.gov
email: mmax@dir.nidcr.nih.gov
phone: 496-5483 x405

Alternate interview candidates:

Questions for experts on therapy for neuropathic pain:

Background for questions: Abbott calls ABT-594 a cholinergic channel modulator. Others in the literature call it a neuronal nicotinic receptor agonist. It should be noted that animal studies are all studies of nociceptive pain (caused by injuious stimuli, eg. heat) as opposed to neuropathic pain (caused by never injury).

1. It is my understanding the tricyclic antidepressants, carbamazepine, gabapentin and amitriptyline are widely used in the treatment of neuropathic pain. Are these drugs sufficient for the need?

CONFIDENTIAL
JH 002198

2. There are a number of adjuvant analgesics in clinical development that could compete with nicotinic acetylcholine receptor agonists. Some examples are pregabalin (Parke-Davis) in Phase III trials, GV196771 (Glaxo) in Phase II, mamantine (Merz) in Phase II, ABT-924 (Abbott) which of these--or others that you know of--show special promise for neuropathic pain?

3. A variety of nicotinic acetylcholine receptor agonists such as nicotine, epibatidine and the azetidinyl ether, (R)-5-(2-azetidinylmethoxy-2-chloropyridine (ABT-594) appear to possesses significant efficacy in preclinical models of pain. Are any of these in clinical trials? Are any especially promising? Is the nicotinic acetylcholine receptor the same as the cholinergic channel? How do nicotinic acetylcholine receptor agonists stack up against the other kinds of drug candidates (above)?

4. It has been reported that some of the nicotinic acetylcholine receptor agonists have a small therapeutic window, which I'll define here as:

(conc. for intolerable side effects)/(conc. for efficacy)

5. What is an acceptable therapeutic window for pain relievers in general, neuropathic pain relievers?

6. It seems to me that for pain relievers, where a patient might take many more pills than recommended, a therapeutic window of two to three is not sufficient? Are diabetic patients more compliant? Comment. What size of therapeutic window does the FDA look for in pain medications?

7. Is there an important issue we haven't discussed or important question I haven't asked? What is it and what is your opinion?

Articles which the interview candidates have written as reference for interviews:

Belgrade MJ
(*Good interview candidate*)
Fairview Pain Management Center, Fairview-University Medical Center,
Minneapolis, MN 55454, USA. mbelgra1@fairview.org
Neuropathic pain can seem enigmatic at first because it can last indefinitely and often a cause is not evident. However, heightened awareness of typical characteristics, such as the following, makes identification fairly easy: The presence of certain accompanying conditions (e.g., diabetes, HIV or herpes zoster infection, multiple sclerosis) Pain described as shooting, stabbing, lancinating, burning, or searing Pain worse at night Pain following anatomic nerve distribution Pain in a numb or insensate site The presence of allodynia Neuropathic pain responds poorly to standard pain therapies and usually requires specialized medications (e.g., anticonvulsants, tricyclic antidepressants, opioid analgesics) for optimal control. Successful pain control is

enhanced with use of a systematic approach consisting of disease modification, local or regional measures, and systemic therapy.
PMID: 10576007, UI: 20043307

DIABETES.UWMUniversity of Wisconsin CHS (1-Dec-98)
Promising Choice for Diabetic Neuropathy Pain
Description: A new study led by the University of Wisconsin Medical School has found that a medication now used for controlling seizures is also effective against the pain of diabetic neuropathy -- with fewer and less serious side effects.
12/1/98
RESEARCH IDENTIFIES PROMISING CHOICE FOR MANAGING PAIN OF DIABETIC NEUROPATHY UW researcher says drug is first effective option in more than a decade MADISON -- A new study led by researchers from the University of Wisconsin Medical School has found that a medication now used for controlling seizures is also effective against the pain of diabetic neuropathy -- and produces fewer and less serious side effects than currently available treatments. Gabapentin, an anti-convulsant available in the U.S. for four years, not only significantly reduced pain from chronic neuropathy (due to damaged nerves) but also reduced sleep disturbances, improved mood and enhanced patients? quality of life. The findings are reported in the Dec. 3 edition of the Journal of the American Medical Association. Neuropathy, or nerve damage, is the most common complication of diabetes: up to 45 percent of diabetic patients develop neuropathy in the course of the disease. While some patients report a numbness or tingling sensation, others experience neuropathic pain as a very distressing ╜pins and needles╜ sensation or one similar to receiving a series of electric shocks. Diabetic neuropathy pain most often affects the feet and ankles and to a lesser extent the legs above the knees and the arms. Poor control of blood sugar leads to nerve damage, which in turn may prompt the development of neuropathy. ╜This is the first study in more than 10 years to show there?s another promising agent for treatment of nerve pain from diabetes,╜ said principal investigator Dr. Miroslav Backonja, associate professor of neurology at University of Wisconsin Medical School and a pain pecialist at UW Hospital and Clinics. ╜Gabapentin is a very welcome addition to our options for pain control. It is well-tolerated by most patients and stands apart from other drugs in that it doesn?t interfere with other medications.╜ In the study, 165 diabetic patients at 20 medical centers were randomly assigned to either an experimental group, which received gabapentin, or the control group, which received a placebo. All of the patients had a one- to five-year history of pain attributed to diabetic neuropathy. The study was double-blind, meaning neither the patients nor the researchers knew who was taking which agent. At the end of the eight-week study period, patients turned in daily diaries they had kept to monitor pain and sleep interference and also completed an assessment of their overall well-being. Researchers independently completed their own clinical assessment of change. Approximately 60 percent of the patients on gabapentin reported at least moderate improvement in their pain, while only 33 percent of placebo patients did. In addition, the medication proved to be well-tolerated; two-thirds of the gabapentin patients were able to take the highest dosage tested in the study. The most common side effects were dizziness and sleepiness, although they typically were of mild or moderate intensity. Backonja and his colleagues also found in the study that patients may get pain relief at dosages less than the maximum (3600 mg) tested, and clinicians are advised to adjust dosages based on their observations of individual patients. Backonja said gabapentin?s

"metabolic simplicity" – meaning it does not interact with or compete with other substances -- is important for diabetics,
who frequently take several medicines. Gabapentin can be used alone or with other drugs to control pain. About three percent of Wisconsin residents have diabetes, according to the state Division of Health. The Centers for Disease Control estimates that 15.7 million Americans have the disease; only 10 million have been diagnosed. Its incidence is increasing.

High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. Nelson KA, Park KM, Robinovitz E, Tsigos C, Max MB Pain and Neurosensory Mechanisms Branch, National Institute of Dental Research, National Institutes of Health, Bethesda, MD 20892-1258, USA.N-methyl-D-aspartate (NMDA) receptor antagonists relieve neuropathic pain in animal models, but side effects of dissociative anesthetic channel blockers, such as ketamine, have discouraged clinical application. Based on the hypothesis that low-affinity NMDA channel blockers might have a better therapeutic ratio, we carried out two randomized, double-blind, crossover trials comparing six weeks of oral dextromethorphan to placebo in two groups, made up of 14 patients with painful distal symmetrical diabetic neuropathy and 18 with postherpetic neuralgia. Thirteen patients with each diagnosis completed the comparison. Dosage was titrated in each patient to the highest level reached without disrupting normal activities; mean doses were 381 mg/day in diabetics and 439 mg/day in postherpetic neuralgia patients. In diabetic neuropathy, dextromethorphan decreased pain by a mean of 24% (95% CI: 6% to 42%, $p = 0.01$), relative to placebo. In postherpetic neuralgia, dextromethorphan did not reduce pain (95% CI: 10% decrease in pain to 14% increase in pain, $p = 0.72$). Five of 31 patients who took dextromethorphan dropped out due to sedation or ataxia during dose escalation, but the remaining patients all reached a reasonably well-tolerated maintenance dose. We conclude that dextromethorphan or other low-affinity NMDA channel blockers may have promise in the treatment of painful diabetic neuropathy.

KLOTZ DEPOSITION EXHIBIT 27

D'S EXHIBIT 811

Klotz
EXHIBIT NO. 27
5-16-07
MICHELLE KEEGAN

From: Lynn C. Klotz [LynnKlotz@compuserve.com]
Sent: Friday, July 21, 2000 7:39 PM
To: Blewitt, Stephen
Subject: Moellering interview

Attached is the Moellering interview. I will do the Nelson one tomorrow.

--Lynn

File:ketolides-moellering

Robert Moellering interview on colchicine-site binding agents

Robert C. Moellering, Jr., MD
Physician in Chief
Department of Medicine
Beth Israel Deaconess Medical Center, and
Professor Harvard Medical School
Tel: 617-632-7437
e-mail: rmoeller@caregroup.harvard.edu

Dr. Moellering is an expert on antimicrobial therapy. His major interests include the mechanism of action and mechanisms of resistance to antimicrobial agents. He is or has served as editor of three major antimicrobial and infectious disease journals.

He was the senior author of a recent article entitled "In-vitro Activity of the New Ketolide Antibiotic HMR 3647 Against Gram-positive Bacteria." (J Antimicrob Chemother 1998, Sep; 42(3): 297-301).

Interview

The interview summary below was typed from handwritten notes and memory shortly after the interview, and is therefore subject to error in details normal to this process. Some of the interview has been rearranged for clarity. The interviewers comments and questions are in italics, Dr. Moellering's comments in normal type. This interview summary should remain **confidential** within John Hancock, as I did not ask if they could be disseminated beyond Hancock and the interviewee has had no chance to comment and correct the summaries.

Before we get to ketolides, what other new classes of antibiotics show promise against resistant gram-positives?

The development pipeline opens and closes. In the last year and a half nothing new and different has entered the pipeline.

Let me review some of the recent ones to reach the market. These antibiotics are being developed as substitutes for use in vancomycin-resistant bacteria.

Synercid (Aventis) is an intravenous antibiotic which has just entered the market. It is not the greatest drug, but does have activity against vancomycin-resistant Staph. I doubt that it will reach sales per year of $100 to $150 million.

Zyvor or another antibiotic just on the market. It can be administered orally and intravenously. The problem with this antibiotic is that it is bacteriostatic (*doesn't kill bacteria, just prevents them from proliferating*) not bacteriocidal. You have to wait a long time to kill bacteria.

Pharmacia has an oxazolidnone antibiotic, Zyvox is the brand name, which has good activity against gram-positive bacteria and is just on the market. There are at least five companies developing oxazolidnone antibiotics.

Daptinomycin is a complex lipopeptide antibiotic which Cubist acquired from Lilly. It is intravenously administered. It kills bacteria by damaging the membrane. (*Dr. Moellering brought up daptinomycin without any prompting from me, which indicates to me that it is at least on the radar screen of new promising agents.*)

Is it one of those peptides that creates pores in membranes so that the cellular constituents leak out?

No, it alters the transport of ions across the membrane.

Would daptinomycin be expensive to manufacture since it is a complex lipopeptide?

It is a modified natural product. (*So manufacturing cost may not be an issue.*)

Daptinomycin is a second line of defense when standard therapies don't work.

Lilly also has a vancomycin substitute which is administered intravenously. It is in limited Phase III clinical trials because of toxicity concerns since it has a very long half-life of 150 hours in the body.

Glycocycline derivatives are IV administered tetracyline derivatives. They are highly effective against gram-positive and gram-negative bacteria, but have intestinal toxicity when given orally.

All these antibiotics I have mentioned have been known for three or four years, so they don't represent new promising agents just entering the pipeline.

One antibiotic, Zyricin, has just been abandoned in clinical trials. It had both efficacy and toxicity problems.

What about ketolides?

The Aventis antibiotic, Ketek, has just been approved in Europe. It has not yet been approved in the US yet. (*According to Abbott, an NDA for Ketek has been filed in the US.*)

Abbott's ketolide has more promise than Aventis'. I am talking relative here. Ketolides have pluses and minuses because they are modified macrolide antibiotics. For example, erythromycin is a macrolide. All macrolides cause a degree of G.I. toxicity when given orally. Also bacteria have many resistance mechanisms against macrolides.

To circumvent resistance is the reason ketolides were developed. The two major resistance mechanisms are (1) an efflux mechanism that pumps macrolides out of the bacterium, and (2)

methylation of an adenine at the ribosomal binding site for the antibiotic which prevents the antibiotic from binding. (*A major mechanism of a number of antibiotics is binding selectively to bacterial ribosomes to prevent translation of messenger RNA into protein.*) There are also a number of minor resistance mechanisms to macrolides. The existence of several resistance mechanisms makes it easier for non-resistant bacteria to develop resistance.

Ketolides are modifications of macrolides that avoid the major resistance mechanisms. First, a ketone group is attached to the "active" site on the macrolide which allows the antibiotic to avoid efflux (doesn't induce the efflux mechanism). It had been thought that the active site couldn't be modified and activity retained. It was surprising to find that macrolides could be modified with a ketone at the active site and still retain activity. Second, other macrolide modifications in kletolides make them bind strongly to ribosomes, so the adenine methylation does not prevent binding necessary for activity.

One problem with ketolides is that they have a limited range of bacterial-species activity, which will probably limit their usefulness to respiratory infections.

In business terms, will that make their market insubstantial?

The respiratory infection market is very big; it includes sinusitis, bronchitis and pneumonia.

Aventis claims their ketolide will reach $1 billion in sales. Do you think that is possible?

To attain a $1 billion market, two things must happen. They must unseat erythromycin and they must out compete the new fluoroquinolones which are going after the same market. There is a scenario where ketolides may find significantly greater use than fluoroquinolones. Clinicians are familiar with macrolides and know that they are safe. They also know that they may develop resistance and have been living with that. They may wish to use fluoroquinolones sparingly to retard the development of resistance in them and use them primarily as a second line of defense.

Regarding Abbott's ketolide, I haven't seen the clinical trial data, but if they have better activity than erythromycin against *H. Influenzae*, that would give them a big market boost. (*Note: Abbott's Phase II data indicate a 92% effectiveness (overall eradication) against H. Influenzae. How does this compare to erythromycin?)*

Is there an important issue we haven't discussed or important question I haven't asked?

No, I think we have pretty much covered it.

<u>Additional questions for Abbott from what was learned from this interview:</u>

Your Phase II clinical data indicates a 92% effectiveness (overall eradication) against *H. Influenzae*. How does this compare to erythromycin? If more effective than erythromycin, how do you see that affecting market size?

Do you see a competitive threat from the new peptide antibiotics such as Daptinomycin?
To attain a $1 billion market for a ketolide as Aventis predicts, one of the experts we interviewed thought that two things must happen. It must unseat erythromycin, and it must out compete the new fluoroquinolones which are going after the same market. Do you agree with that statement? If so, how do you see it happening?

KLOTZ DEPOSITION EXHIBIT 28

D'S EXHIBIT L

K6 F2
EXHIBIT NO. 28
5-16-07
MICHELLE KEEGAN

Research Analysis Report

The Changing Face of Antihistamines And Cardiac Adverse Drug Reactions : A Clinical Perspective

WIQAR A SHAIKH*

Recent times have witnessed a qualitative shift in the recognition and management of adverse drug effects. Many of them occur in organs that are unconnected to the primary target of pharmacological action. Out of these, cardiac side-effects have drawn particular attention because of their potential to cause death.

Starting with the early observations on antibiotics such as macrolides, followed by fluoroquinolones and others, the focus has now shifted to the antihistamine class of drugs which are used extensively by patients all over the world, thanks to the ever increasing levels of environmental pollution. The occurrence of prolonged QTc interval following treatment with terfenadine leading to ventricular tachycardia of torsades de points variety with a potentially fatal outcome has forced many regulatory authorities of the world to clamp a ban the use of this drug.

Alerted by these developments, studies on a new member , followed by fluoroquinolones and others, the focus has now shifted to the antihistamine class of drugs which are used extensively by patients all over the world, thanks to the ever incresing levels of envrionmental pollution. The occurrence of prolonged QTc interval following treatment with terfenadine leading to ventricular tachycardia of torsades de points variety with a potentially fatal outcome has forced many regulatory authorities of the world to clamp a ban use of this drug.

Alerted by these developments, studies on a new member of non-sedating antihistamine class viz, fexofenadine, have been reviewed especially because of the structural similarity between terfenadine and fexofenadine. It is now clear that despite the closeness of its chemical structure to terfenadine fexofenadine behaves in a different manner and does not affect the electro-physiology of the heart muscle tissue, as proved by data from extensive clinical trials as well as membrane models *in vitro*. Interestingly, the solitary false alarm that was sounded on the drug by a group of workers in the Netherlands was later rectified by the same group. Clinically speaking, the cardiovascular safety of fexofenadine has been convincingly demonstrated at various dose levels and various time intervals, alone and together with other drugs of potential toxigenicity. All things put together, it appears reasonable to conclude that fexofenadine is free from cardiovascular ADRs of clinical significance. It could also be concluded that cardiac side-effects of antihistmines is not a class effect.

With the steady flow of newer chemical entities entering modern therapeutics in various domains, there is emerging a spectre of adverse drug reactions from some of the least expected quarters, unconnected with the organs targeted for therapy. By and large most of the side-effects of commonly prescribed oral agents reported hitherto have related to the gastro-intestinal tract, while other organs like the liver, kidney, haemopoietic system, etc, have been affected relatively less frequently. The recently reported instances of cardiovascular side-effects with diverse agents such as antihistamines and antibiotics used in ambulatory practice marks a watershed development in the clinical domain of seemingly routine therapy for ordinary clinical conditions[1].

Early pointers — An early pointer to such unexpected side-effects in fact came from antibiotics. A wide array of this class of drugs is being used in our country for the treatment of an equally wide variety of infections. But the lion's share goes to ambulatory therapy for community acquired respiratory tract infections, where macrolides have deservedly made their mark all over the world. The prototype macrolide, erythromycin, which has been in use for nearly half a century, came under fresh scrutiny when certain cardiac side-effects, such as delayed ventricular repolarisation characterised by prolonged QTc interval, a pre-condition for the development of fatal ventricular tachycardias, were reported. The incidence increased on co-administration with other drugs with a similar propensity[2]. Warnings on drug interaction were soon established and widely disseminated.

Of the other classes of anti-infectives, modern fluroquinolones are also making their impact felt in the management of community acquired respiratory tract infections, thanks to their broad antibacterial spectrum especially against Gram-positive microbes such as *Streptococcus pneumoniae*. But there was a surprise here as well when sparfloxacin, a modern quinolone, was reported to produce cardiac side-effects similar to erythromycin[3]. It is now generally accepted that if there are pre-existing cardiovascular risk factors in patients receiving sparfloxacin, such therapy might pave the way for ventricular tachycardia, as it happened in some patients who were part of a post-marketing surveillance study[3].

Another commonly used class of drugs that sprang a surprise from a cardiovascular point of view were the antihistamines. Suspicions had prevailed with astemizole and terfenadine for a long time but with the accumulating evidence from several centres across the globe, the regulatory authorities had to take action eventually. It is now well known that an important member of the non-sedating class of newer antihistamines, namely terfenadine, has been withdrawn from the market in several countries because of the same potentially lethal cardiovascular side-effect viz, QTc prolongation[4].

Uppsala experience—The WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, tracked the experience on the risks of five antihistamines viz, acrivastine, astemizole, cetirizine, loratadine and terfenadine. Sales data from 17 countries were available and covered 9976 adverse drug reaction reports as calculated in terms of reports per million defined daily doses (DDDs) sold.

The overall reporting rate profiles for all five antihistamines had similarities in the sense that the rates per body system organ class were lower than 0,25 reports per million DDDs sold. Adverse effects relating to CNS, psychiatric, special sensory and general reactions accounted for most of the reports. With regard to cardiotoxicity, a break up of the reports is presented in Table 1.

Table 1— *Cardiac Rate and Rhythm Disorders*

Drug	Total rate and rhythm disorders	Selected reactions*	Cardiac deaths/ sudden death
Acrivastine	3	1	0
Astemizole	233	110	8
Cetirizine	15	19	2
Loratadine	266	106	13
Terfenadine	864	429	98

*Arrhythmia, ventricular arrhythmia, cardiac arrest, ventricular fibrillation, QT prolongation, supraventricular tachycardia, ventricular tachycardia, torsades de pointes

Based on the above data, it was pointed out by the Uppsala investigators that "some of the alternatives to terfenadine may have a

*Hony Allergist, Bombay Hospital & Medical Research Centre, Mumbai 400020

similar problem, suggesting that thorough considerations of the comparative benefit risk profile of all non-sedating antihistamines is wise[4].

Not a class-effect — There were fears expressed in some quarters that the cardiac side-effects of antihistamines might be a problem associated with this class of drugs as a whole, but this does not appear to be the case[6]. This was also proven in elaborate comparative studies in which the sensitive index of antihistamine ED50[7] was used as a measure of drug activity. The lowest dose of the antihistamine required to produce detectable prolongation of QTc interval was compared to the dose required to inhibit by 50% the peripheral bronchospasm elicited by histamine at 10 microgrammes/kg administered intravenously. Using this method on a host of antihistamines viz, astemizole, norastemizole, carebastine, ebastine, cetirizine, and terfenadine the investigators observed that only astemizole, ebastine and terfenadine were arrhythmogenic in this model, thus ruling out any possibility of a class effect of this category of drugs on the cardiac tissue.

Ebastine (an antihistamine not available in India) is known to block potassium channels in the myocardial tissue, but this is not as pronounced as with terfenadine[8]. In rat ventricular myocytes, the inhibitory effects of terfenadine were more marked than those with ebastine and epinastine[9]. When coadministered clinically with ketoconazole, QTC prolongation was observed to occur with cetirizine and ebastine as evident in serial ECG or Holter monitoring. These effects were however not as pronounced as with terfenadine[10].

Large data base — Against this background, the recent findings on fexofenadine, which has now been made available globally, and is rapidly filling the void left by the departure of terfenadine, prove interesting and thus merit a closer look. As a truly non-sedating agent, it is also devoid of antimuscarinic side-effects. It is important to view the pharmacokinetics of fexofenadine closely in this context, because it is actually the acid metabolite of terfenadine[11], a fact that has raised some questions regarding its freedom from similar side-effects.

It was precisely because fexofenadine is the acid metabolite of terfenadine, its effects on the eletrocardiogram of treated patients had to be very carefully monitored and evaluated during its clinical development prior to registration. In a review of the available clinical trial data on fexofenadine, the absence of any adverse effect of the drug on the electrocardiographic findings of the patients was brought out with special emphasis[12]. In controlled trials with approximately 6000 persons, no case of fexofenadine-associated torsade de pointes was observed. It is important to review the available data more closely to reconfirm the cardiovascular safety of fexofenadine.

Material and Method

Two double-blind, randomised, 2-week placebo-controlled parallel studies were conducted with a total of 1,160 patients with seasonal allergic rhinitis, of whom 870 received fexofenadine and 290 received placebo[13,14]. Doses of 40,60 120 and 240 mg of the drug given twice daily were compared with placebo. Electrocardiographs were studied at 1-3 hours following the final dose when plasma levels of the drug were expected to be the highest. Mean changes from baseline were compared across doses and for each dose compared with placebo. Since the two studies were identical in their design, the data could be pooled for scrutiny (Table 2).

Observations and Discussion

The results that emerged were indeed striking in demonstrating the cardiovascular safety of fexofenadine:

- There was no statistically significant increase in mean QTc with fexofenadine as compared to placebo.
- There was no statistically significant increase in mean QTc with increasing doses of fexofenadine.
- There was no dose-response relation between QTc and the dose of fexofenadine.
- There was no statistically significant change from baseline in QTc for any individual dose of fexofenadine.
- There was no statistically significant difference in change from bseline QTc between placebo and any individual dose of fexofenadine.

Table 2 — *Mean QTc and Mean QTc Change from Baseline in Patients with Seasonal Allergic Rhinitis Treated with Fexofenadine (n=1160)*

Treatment (twice daily)	No of cases	Baseline QTc (ms)	End study QTc (ms)	Change from basline QTc
Placebo	285	409	408	-1.6
Fexofenadine 40 mg	144	411	410	-1.2
Fexofenadine 60 mg	283	410	409	-0.5
Fexofenadine 120 mg	286	410	410	0.3
Fexofenadine 240 mg	145	409	409	0.1

QTc outliers and drug interactions — In clinical trials with fexofenadine for seasonal allergic rhinitis, particular attention was paid to those cases where the maximum QTc value measured exceeded 440 milliseconds (ms), with an increase of greater than 10 ms from the baseline value (called 'outlier' QTc value). The incidence of such cases is presented in Table 3. The salient observations in this regard are:

Table 3 — *Incidence of QTc Outliers in Seasonal Allergic Rhinitis Patients Treated with Fexofenadine (n=1160)*

Treatment (twice daily)	QTc outlier incidence n/N (%)	Maximum QTc interval (ms)
Placebo	17/285 (6.0%)	484
Fexofenadine 40 mg	7/144 (4.9%)	488
Fexofenadine 60 mg	18/283 (6.4%)	484
Fexofenadine 120 mg	19/286 (6.6%)	479
Fexofenadine 240 mg	8/145 (5.5%)	480
Fexofenadine all doses	52/858 (6.0%)	488

- The incidence of outlier values was similar in fexofenadine and placebo groups.
- The incidence did not increase with increasing dose of fexofenadine.
- The range of QTc outlier values were similar in fexofenadine and placebo groups.

The prolongation of QTc interval due to terfenadine was attributed to the excessive accumulation of the drug arising out of coadministration with other drugs that interfere with its metabolism by hepatic cytochromal enzymes responsible for CYP3A4 metabolic pathways[15]. As a result, drug interaction studies have assumed considerable significance in ruling out cardiac toxicity by potential drug candidates. The reference drugs that are known to compete for these metabolic pathways are ketoconazole and erythromycin. Accordingly fexofenadine was studied for its potential interaction with these drugs in healthy volunteers in open-label, multiple-dose, randomised cross-over studies for a 6.5-day dosing period[16]. There was no increase in QTc interval when fexofenadine was combined with these agents (Table 4).

Long term safety — Since many patients with allergic rhinitis tend to consume antihistamines over prolonged periods of time, the importance of long term safety studies has been increasingly recognised in recent times. Fexofenadine was studied for safety over periods ranging from 3 months to 12 months of continuous administration in three parallel, placebo- controlled studies[16]. There was no difference between placebo controls and fexofenadine treated patients with regard to the change in QTc from baseline characteristics nor was the incidence of outliers any different between the placebo and drug-treated patients (Table 5).

It must be emphasised that in controlled clinical trials covering

Table 4 — *Drug Interaction Studies: Fexofenadine + Erythromycin/Ketoconazole*

Treatment	No of cases	Baseline QTc (ms)	Day 7 QTc (ms)	Change from baseline	P value
Fexofenadine 120 mg twice daily + erythromycin 500 mg thrice daily	19	391 ± 23	393 ± 24	1.6 ±11.1	0.5285
Fexofenadine 120 mg twice daily + ketoconazole 400 mg once daily	23	396 ± 14	399 ± 15	3.1 ± 10.9	0.1812

Table 5 — *Long Term Safety Studies Fexofenadine*

Duration	Treatment	No of cases	Baseline QTc (ms)	End study QTc (ms)	Change from baseline	Incidence of outlier QTc (%)
3 months	Placebo	14	413	404	-8.8	0
	Fexofenadine 80 mg bid	27	408	405	-2.3	0
6 months	Placebo	209	401	401	0.3	8.6
	Fexofenadine 60 mg bid	216	402	403	0.9	7.4
12 months	Placebo	233	397	403	5.6	9.9
	Fexofenadine 240 mg od	231	398	401	3.0	9.5

more than 6000 patients all over the world, not a single episode of torsade de pointes ventricular tachycardia has been reported, even after 12 months of continuous drug administration. In yet another study[17] 432 patients with chronic urticaria were given fexofenadine at a daily dosage of 180 mg for a variable period of 14 days to 3 months. Cardiac status and ECG were evaluated prior to and during the treatment period. There was no evidence of QTc prolongation or the development of ventricular tachycardia in any patient. There are indeed strong testimonies to the cardiovascular safety of fexofenadine against the backdrop of significant risk posed by other antihistamines.

The basic cellular mechanism by which some antihistamines like terfenadine cause QTc prolongation has now been studied extensively. The ionic channels in the myocardial cell wall responsible for the movement of potassium, especially the I_{Kr} type, have been shown to be blocked by terfenadine. It has also been demonstrated that these potassium channels are totally unaffected by fexofenadine, which goes to explain the absence of clinical cardiovascular toxicity with fexofenadine in contrast to terfenadine and other antihistamines [18]. In this context, it must be mentioned that a false alarm was sounded on fexofenadine with the development of ventricular arrhythmias in a 67-year-old man [19] but the same patient was further studied by the same group of investigators, using sophisticated laboratory techniques to rule out the causative role of the drug. This case is a clear example of how not to jump to conclusions with regard to drug toxicity based on a random report.

References

1 Woosley RL—Cardiac actions of antihistamines. *Ann Rev Pharmacol Toxicol* 1996; 36: 233-52.
2 Naitel S, *et al*—Torsades de pointes caused by erthromycin. *Chest* 1994; 105: 368-72.
3 Rubinselin E—Safety profile of sparfloxacin in the treatment of respiratory tract infections. *J Antimicrob Chemother* 1996; 37 supple A: 145-60.
4 Jaillon P, Morganroth J, Brumpt I, *et al*—Overview of electrocardiographic and cardiovascular safety data for sparfloxacin. *J Antimicrob Chemother* 1996; 37 suppl A: 161-7.
5 Lindquist M, Edwards I R—Risks of non-sedating antihistamines. *Lancet* 1997; 349: 1322.
6 Himmel MH, *et al*—Dangers of nonsedating antihistamines. *Lancet* 1997; 350 :69.
7 Hey JA, del Prado M, Sherwood J, Kreutner W, Egan RW—Comparative analysis of the cardiotoxicity proclivities of the second generation antihistamines in an experimental model predictive of adverse clinical ECG effects. *Arzneimittelforsch* 1996; 46 : 153 -8.
8 Ko CM, Ducic I, Fan J, Shuba YM , Morad M—Suppression of mammalian potassium channel family by ebastine. *J Pharmacol Exp Ther* 1997; 28 : 233-44.
9 Ohtani H, Hanada E, Hirota M, Sato H, Kotaki H, Sawada Y, *et al*—Inhibitory effects of antihistamines epinastine, terfenadine and ebastine on potassium currents in rat ventricular myocytes. *J Pharm Pharmacol* 1999; 51: 1059-63.
10 Moss AJ, Chaikin P, Garcia JD, Gillen M, Roberts DJ, Morganroth J—A review of the cardiac systemic side effects of antihistamines: ebastine. *Clin Exp Allergy* 1999; 29 suppl 3: 200 -5.
11 Markham A, Wagstaff AJ – fexofenadine. *Drugs* 1998; 55; 269-74.
12 Pratt CM, Mason J, Russell T, Reynolds R, Ahlbrandt R—Cardiovascular safety of fexofenadine HCl. *Am J Cardiol* 1999; 83: 1451- 4.
13 Bernstein D, Schoenwetter WF, Nathan RA, Storms W, Ahlbrandt R, Mason J—Efficacy and safety of fexofenadine HCl for seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 1997; 79 : 443-8.
14 Bronsky EA, Falliers CJ, Kaiser HB, Ahlbrandt R, Mason JM—Effectiveness and safety of fexofenadine, a new non-sedating H_1-receptor antagonist in the treatment of fall allergies. *Allergy Asthma Proc* 1998; 19: 135-41.
15 Honig PK, Woolsey RL, Zamani K, Conner DP, Cantilena LR—Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. *Clin Pharmacol Ther* 1992; 52: 231-8.
16 Hoechst Marion Roussel—Fexofenadine HCl: integrated summary of safety. NDA 20-625. Data on file. Kansas City, USA: Hoechst Marion Roussel.
17 Dhar S—Fexofenadine and cardiovascular safety. *Br J Dermatol* 2000 (in press).
18 Scherer CR, Lerche C, Pinto YM, Busch AE, Steinmeyer K – The antihistamide fexofenadine does not affect I_{Kr} currents in a patient reported to have fexofenadine induced cardiac arrhythmia. *Biophys J* 2000; 78 : 342A.
19 Pinto YM, van Gelder IC, Heeringa M, Crijns HJGM—QT lengthening and life-threating arrhythmias associated with fexofenadine. *Lancet* 1999; 353: 980.

KLOTZ DEPOSITION EXHIBIT 29

D’S EXHIBIT M

U.S. Food and Drug Administration

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

SUMMARY OF SAFETY-RELATED DRUG LABELING CHANGES APPROVED BY FDA June 2000

(Posted: August 11, 2000)

Note: The following summaries include only those safety-related sections that have been modified, and therefore do not contain all the information needed for safe and effective prescribing. Contact the manufacturer for the complete labeling/package insert.

NB: Comparison made to 2000 *Physicians' Desk Reference* (PDR), if drug's labeling included in the PDR.

Quick Reference:

(Click on name of the product to go directly to the summary.)

ACCOLATE (zafirlukast)	**AMBISOME (amphotericin B)**	**ANDROGEL (testosterone gel)**	**AQUASOL A (vitamin A palmitate)**
ATACAND (candesartan)	**BIAXIN (clarithromycin)**	**CIPRO (ciprofloxacin)**	**COSMEGEN (dactinomycin)**
CYTOTEC (misoprostol)	**DEPAKOTE, DEPACON & DEPAKENE (divalproex sodium, valproate sodium & valproic acid))**	**EFFEXOR XR (venlafaxine HCl)**	**EVISTA (raloxifene HCl)**
FOSCAVIR (foscarnet sodium)	**GEMZAR (gemcitibine HCl)**	**GENOTROPIN (somatropin)**	**IONOSOL MB, IONOSOL B & IONOSOL T**

			(electrolytes)
ISMO (isosorbide mononitrate)	LUVOX (fluvoxamine maleate)	MELLARIL (thioridazine HCl)	NAVELBINE (vinorelbine)
NOLVADEX (tamoxifen citrate)	NORMOSOL-R (electrolytes)	ORTHO-CYCLEN & ORTHO TRI-CYCLEN (norgestimate/ ethinyl estradiol)	ORTHO-NOVUM (norethindrone/mestranol)
PRAVACHOL (pravastatin sodium)	PREVACID (lansoprazole)	QUINAGLUTE DURA-TABS (quinidine gluconate)	REGLAN (metoclopramide)
RHINOCORT (budesonide)	SEREVENT (salmeterol xinafoate)	SERZONE (nefazodone HCl)	SODIUM ACETATE
SODIUM PHOSPHATE	STERILE WATER	TICLID (ticlopidine HCl)	TONOCARD (tocainide HCl)
UREAPHIL (sterile urea)			

Return to Quick Reference

ACCOLATE (zafirlukast) Tablets
[June 12, 2000: AstraZeneca]

[Other labeling changes not appearing in 2000 PDR: Feb00, Sep99]

PRECAUTIONS:

Information for patients: Third paragraph, third sentence revised -

"Patients should be told that a rare side effect of Accolate is elevation of liver enzymes and that if they experience signs and/or symptoms of liver dysfunction (e.g., right upper quadrant abdominal pain, nausea, fatigue, lethargy, pruritus, jaundice, and flu-like symptoms), they should contact their physician immediately."

Replaced with revisions incorporated below -

"Patients should be told that a rare side effect of Accolate is hepatic dysfunction, and to contact their physician immediately if they experience symptoms of hepatic dysfunction (e.g., right upper quadrant abdominal pain, nausea, fatigue, lethargy, pruritus, jaundice, flu-like symptoms, and anorexia)."

Hepatic: Section revised -

Rarely, elevations of one or more liver enzymes may occur during Accolate therapy. Most of these have been observed in clinical trials with Accolate at doses four times higher than the recommended dose. The clinical significance of these elevations are unknown. Cases of symptomatic hepatitis and hyperbilirubinemia without other attributable cause, have been reported from the post-marketing experience in patients who have received the recommended dose of Accolate (40 mg/day). In rare cases, patients have progressed to hepatic failure. In most, but not all patients, the clinical symptoms abated and the liver enzymes returned to normal or near normal after stopping Accolate. If clinical signs or symptoms of liver dysfunction (e.g., right upper quadrant abdominal pain, nausea, fatigue, lethargy, pruritus, jaundice, and flu-like symptoms) are noted, it is reasonable to recommend that standard liver tests be obtained and the patient managed accordingly. A decision to discontinue Accolate should be individualized to the patient's condition weighing the risk of hepatic dysfunction against the clinical benefit of Accolate to the patient. (See PRECAUTIONS, Information for Patients and ADVERSE REACTIONS sections.)

Replaced with revisions incorporated below -

"Rarely, elevations of one or more liver enzymes have occurred in patients receiving Accolate in controlled clinical trials. In clinical trials, most of these have been observed at doses four times higher than the recommended dose. The following hepatic events (which have occurred predominantly in females) have been reported from postmarketing adverse event surveillance of patients who have received the recommended dose of Accolate (40 mg/day): cases of symptomatic hepatitis (with or without hyperbilirubinemia) without other attributable cause; and rarely, hyperbilirubinemia without other elevated liver function tests. In most, but not all, postmarketing reports, the patient's symptoms abated and the liver enzymes returned to normal or near normal after stopping Accolate. In rare cases, patients have progressed to hepatic failure.

"If liver dysfunction is suspected based upon clinical signs or symptoms (e.g., right upper quadrant abdominal pain, nausea, fatigue, lethargy, pruritus, jaundice, flu-like symptoms, anorexia, and enlarged liver) Accolate should be discontinued. Liver function tests, in particular serum ALT, should be measured immediately and the patient managed accordingly. If liver function tests are consistent with hepatic dysfunction, Accolate therapy should not be resumed. Patients in whom Accolate was withdrawn because of hepatic dysfunction where no other attributable cause is identified should not be re-exposed to Accolate. (See PRECAUTIONS, Information for patients and ADVERSE REACTIONS sections).

ADVERSE REACTIONS:

Third paragraph revised -

"Rarely, elevations of one or more liver enzymes have occurred in patients receiving ACCOLATE in controlled clinical trials. Most of these have been observed in asymptomatic patients at doses four times higher than the recommended dose. The clinical significance of these elevations are unknown. Cases of symptomatic hepatitis and hyperbilirubinemia, without other attributable cause have been reported from the post-marketing experience in patients who have received the recommended daily dose of ACCOLATE (40 mg/day). In rare cases, patients have progressed to hepatic failure. In most, but not all patients, the clinical symptoms abated and the liver enzymes returned to normal or near normal after stopping ACCOLATE."

Replaced with revisions incorporated below -

"Rarely, elevations of one or more liver enzymes have occurred in patients receiving Accolate in controlled clinical trials. In clinical trials, most of these have been observed at doses four times higher than the recommended dose. The following hepatic events (which have occurred predominantly in females) have been reported from postmarketing adverse event surveillance of patients who have received the recommended dose of Accolate (40 mg/day): cases of symptomatic hepatitis (with or without hyperbilirubinemia) without other attributable cause; and rarely hyperbilirubinemia without other elevated liver function tests. In most, but not all, postmarketing reports, the patient's symptoms abated and the liver enzymes returned to normal or near normal after stopping Accolate. In rare cases, patients have progressed to hepatic failure."

Sixth paragraph revised (new text in italics) -

"Hypersensitivity reactions, including urticaria, angioedema and rashes, with or without blistering, have been reported in association with Accolate therapy. Additionally, there have been reports of patients experiencing agranulocytosis, bleeding, bruising, edema, *arthralgia, and myalgia* in association with Accolate therapy."

Return to Quick Reference

AMBISOME (amphotericin B) Liposome for Injection
[June 16, 2000: Fujisawa]

[Other labeling changes not appearing in 2000 PDR: Jan99]

Labeling provides for a new indication - use in the treatment of cryptococcal meningitis in HIV infected patients. Contact the company for a copy of the new labeling/package insert.

Return to Quick Reference

ANDROGEL (testosterone) Gel
[June 7, 2000: Unimed Pharmaceuticals]

PATIENT PACKAGE INSERT:

Patient Information and Instructions for Using Androgel: Who should not take Androgel?
Second bullet revised -

"breast cancer (a rare condition for men)
["heart, kidney, or liver disease" deleted]"

Return to Quick Reference

AQUASOL A (water-miscible vitamin A palmitate) Parenteral

[June 9, 2000: Astra]

INDICATIONS:

Pediatric Use: New third paragraph -

"Vitamin A treatment for deficiency states has been recognized as an especially effective and important therapy in the peditic population. Vitamin A supplementation for deficiency states in this population has been addressed by the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition, by the American Society for Parenteral and Enteral Nutrition, and by the World Health Organization."

WARNINGS:

New paragraph -

"Pediatric Use: Polysorbates have been associated with the E-Ferol syndrome (thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension and metabolic acidosis) in low-birth weight infants."

OVERDOSAGE:

Hypervitaminosis A Syndrome:

2. Specific manifestations: (new text in italics)
"d. Systemic: *hepatotoxicity*, hypomenorrhea, hepatosplenomegaly, jaundice, leukopenia, vitamin A plasma level over 1,200 Units/mL."

DOSAGE AND ADMINISTRATION:

Second paragraph revised (new text in italics) -

"Follow-up therapy with an oral therapeutic multi-vitamin preparation containing 10,000 to 20,000 Units vitamin A for ["persons" deleted] *adults and for pediatric patients* over 8 years old, and 5,000 to 10,000 Units for infants and ["children" deleted] *other pediatric patients under 8 years old*, is recommended daily for two months. *Low-birth-weight infants may require additional vitamin A though the exact dosing in these pediatric patients has not been established.* In malabsorption, the parenteral route must be used for an equivalent preparation."

Return to Quick Reference

ATACAND (candesartan cilexetil) Tablets
[June 14, 2000: Astra]

PRECAUTIONS:

Drug Interactions: Second sentence revised (new text in italics) -

"Because candesartan is not *significantly* metabolized by the cytochrome P450 system and *at therapeutic concentrations* has no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzymes would not be expected."

VERSE REACTIONS:

Post-Marketing Experience: New subsection -

"Other adverse events reported for candesartan cilexetil where a causal relationship could not be established include very rare cases of neutropenia, leukopenia and agranulocytosis."

Return to Quick Reference

BIAXIN (clarithromycin) Granules
[June 5, 2000: Abbott]

ADVERSE REACTIONS:

Post-Marketing Experience: Fifth paragraph revised -

"Rarely, erythromycin and clarithromycin have been associated with ventricular arrhythmias, including ventricular tachycardia and torsades de pointes, in individuals with prolonged Qt_c intervals."

Replaced with revisions incorporated below -

"As with other macrolides, clarithromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes."

Return to Quick Reference

CIPRO (ciprofloxacin) I.V. Solution, Tablets & Oral Suspension
[June 28, 2000: Bayer]

CLINICAL PHARMACOLOGY:

Third sentence, fourth paragraph revised [Tablets & Oral Suspension labeling] (new text in italics) -

"After a 250-mg oral dose, urine concentrations of ciprofloxacin usually exceed ["200 mg/mL" deleted] *200 ug/mL* during the first two hours and are approximately ["30 mg/mL" deleted] *30 ug/mL* at 8 to 12 hours after dosing."

[I.V. Solution & Tablets and Oral Suspension labeling] new eighth and fifteenth paragraphs added respectively -

"Pharmacokinetic studies of the oral (single dose) and intravenous (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (> 65 years) as compared to young adults. Although the C_{max} is increased 16-40%, the increase in mean AUC is approximately 30%, and can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the

elderly. These differences are not considered clinically significant. (See PRECAUTIONS: Geriatric Use.)"

PRECAUTIONS:

Information for Patients: First bullet, first three sentences revised [Tablets and Oral Suspension labeling] (new text in italics) -

"that ciprofloxacin may be taken with or without meals *and to drink fluids liberally*. ["The preferred time of dosing is two hours after a meal. Patients should be advised to drink fluids liberally and not take antacids containing magnesium, aluminum, or calcium, products containing iron, or multivitamins containing zinc." deleted] *As with other quinolones, concurrent administration of ciprofloxacin with magnesium/aluminum antacids, or sucralfate, Videx (didanosine) chewable/buffered tablets or pediatric powder, or with other products containing calcium, iron or zinc should be avoided. These products may be taken two hours after or six hours before ciprofloxacin.*"

Drug Interactions: Third paragraph, first sentence revised [Tablets & Oral Suspension labeling] (new text in italics) -

"Concurrent administration of ["ciprofloxacin" deleted] *a quinolone, including ciprofloxacin,* ["with antacids containing magnesium, aluminum, or calcium; with sucralfate or divalent and trivalent cations such as iron may substantially interfere with the absorption of ciprofloxacin, resulting in serum and urine levels considerably lower than desired." deleted] *with multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, Videx (didanosine) chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc may substantially decrease its absorption, resulting in serum and urine levels considerably lower than desired.* ["To a lesser extent this effect is demonstrated with zinc-containing multivitamins." deleted] (See DOSAGE AND ADMINISTRATION for concurrent administration of these agents with ciprofloxacin.)

New fourth paragraph -

Histamine H_2-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

Geriatric Use: New subsection added [I.V. Solution & Tablets and Oral Suspension] -

"In a retrospective analysis of 23 multiple-dose controlled clinical trials of ciprofloxacin encompassing over 3500 ciprofloxacin treated patients, 25% of patients were greater than or equal to 65 years of age and10% were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals on any drug therapy cannot be ruled out. Ciprofloxacin is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. No alteration of dosage is necessary for patients greater than 65 years of age with normal renal function. However, since some older individuals experience reduced renal function by virtue of their advanced age, care should be taken in dose selection for elderly patients, and renal function monitoring may be useful in these patients. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)"

DOSAGE AND ADMINISTRATION:

Fourth paragraph, first sentence revised [Tablets and Oral Suspension labeling] (new text in italics) -

"In acute uncomplicated cystitis in females, the usual dosage is 100-mg *or 250-mg* every 12 hours."

Under "**DOSAGE GUIDELINES**" table, the section for "Urinary Tract Infection, Acute Uncomplicated" -

"or 250-mg" was added to the unit dose column.

See Instructions To The Pharmacist for Use/Handling of Cipro Oral Suspension: New last sentence added -

"Cipro (ciprofloxacin) 5% and 10% Oral Suspension should not be administered through feeding tubes due to its physical characteristics."

The paragraph with the heading " **Concurrent Use With Antacids or Multivalent Cations:**" has been deleted and replaced with the sentence -

"Ciprofloxacin should be administered at least 2 hours before or 6 hours after magnesium/aluminum antacids, or sucralfate, Videx (Didanosine) chewable/buffered tablets or pediatric powder for oral solution, or other products containing calcium, iron or zinc."

Instructions To The Patient For Taking Cipro Oral Suspension: Information concerning shaking the bottle before each use and "the product can be used" was added to the following paragraph to read:

"Swallow the prescribed amount of suspension. Do not chew the microcapsules. Reclose the bottle completely after use according to the instructions on the cap. Shake vigorously each time for approximately 15 seconds. The product can be used for 14 days when stored in the refrigerator or at room temperature (below 86°F). After treatment has been completed, any remaining suspension should not be reused."

Return to Quick Reference

COSMEGEN (dactinomycin) Injection
[June 7, 2000: Merck]

Labeling extensively revised. Contact the company for a copy of the new labeling/package insert.

Return to Quick Reference

CYTOTEC (misoprostol) Tablets

[June 22, 2000: G.D. Searle]

CONTRAINDICATIONS AND WARNINGS:

Boxed Warning revised (new text in italics) -

CYTOTEC (MISOPROSTOL) ADMINISTRATION BY ANY ROUTE IS CONTRAINDICATED, BECAUSE IT CAN CAUSE ABORTION, IN WOMEN WHO ARE PREGNANT (See WARNINGS and PRECAUTIONS). ["Cytotec (misoprostol) is contraindicated, because of its abortifacient property in women who are pregnant. (See Precautions).)" deleted]
Anecdotal reports have been received, primarily from Brazil, of congenital anomalies and reports of fetal death in pregnancies in which misoprostol has been used as an abortifacient. ["Anecdotal reports, primarily from Brazil, of congenital anomalies and reports of fetal death subsequent to misuse of misoprostol as an abortifacient have been received." Deleted]

Two new paragraphs added -

"UTERINE RUPTURE HAS BEEN REPORTED WHEN CYTOTEC WAS ADMINISTERED INTRAVAGINALLY IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE FIRST TRIMESTER OF PREGNANCY.

"UTERINE PERFORATION HAS BEEN REPORTED FOLLOWING ADMINISTRATION OF COMBINED VAGINAL-AND-ORAL CYTOTEC IN PREGANT WOMEN TO INDUCE ABORTION. IN EACH OF THESE REPORTED CASES, THE GESTATIONAL AGE OF THE PREGNANCIES WAS UNKNOWN."

PRECAUTIONS: SPECIAL NOTE FOR WOMEN: Subsection revised -

"Cytotec must not be used by pregnant women. Cytotec may cause miscarriage. Miscarriages caused by Cytotec may be incomplete, which could lead to potentially dangerous bleeding, hospitalization, surgery, infertility, or maternal or fetal death."

Replaced with revisions incorporated below -

"Because of its abortifacient property, Cytotec is contraindicated for use by pregnant women. Cytotec may cause miscarriage if given to pregnant women at any time during pregnancy. Miscarriages caused by Cytotec may be incomplete, which could lead to dangerous bleeding, hospitalization, surgery, infertility, or maternal or fetal death."

ADVERSE REACTIONS:

Gynecological: New third sentence -

"There have been reports in which intravaginal administration of misoprostol in pregnant women resulted in rupture of the uterus and death of the infant. (See boxed CONTRAINDICATIONS AND WARNINGS.)"

Return to Quick Reference

DEPAKOTE (divalproex sodium) Tablets & Capsules
DEPACON (valproate sodium) Injection
DEPAKENE (valproic acid) Capsules & Syrup
[June 19, 2000: Abbott]

[Other information regarding these changes: Letter],
[Other labeling changes not appearing in 2000 PDR: May00]

BOXED WARNING:

PANCREATITIS: New subsection -

"CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD ORDINARILY BE DISCONTINUED. ALTERNATIVE TREATMENT FOR THE UNDERLYING MEDICAL CONDITION SHOULD BE INITIATED AS CLINICALLY INDICATED (See WARNINGS and PRECAUTIONS.)"

WARNINGS:

Pancreatitis: New subsection -

"Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with rapid progression from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use. The rate based upon the reported cases exceeds that expected in the general population and there have been cases in which pancreatitis recurred after rechallenge with valproate. In clinical trials, there were 2 cases of pancreatitis without alternative etiology in 2416 patients, representing 1044 patient-years experience. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated (see BOXED WARNING)."

Somnolence in the Elderly: New subsection -

"In a double-blind, multicenter trial of valproate in elderly patients with dementia (mean age = 83 years), doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. A significantly higher proportion of valproate patients had somnolence compared to placebo, and although not statistically significant, there was a higher proportion of patients with dehydration. Discontinuations for somnolence were also significantly higher than with placebo. In some patients with somnolence (approximately one-half), there was associated reduced nutritional intake and weight loss. There was a trend for the patients who experienced these events to have a lower baseline albumin concentration, lower valproate clearance, and a higher BUN. In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or

discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence (see DOSAGE AND ADMINISTRATION)."

PRECAUTIONS:

General: New last paragraph -

"There are *in vitro* studies that suggest valproate stimulates the replication of the HIV and CMV viruses under certain experimental conditions. The clinical consequence, if any, is not known. Additionally, the relevance of these *in vitro* findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these data should be borne in mind when interpreting the results from regular monitoring of the viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically."

Drug Interactions: Drugs for which a potentially important valproate interaction has been observed:
New first paragraph -

"Amitriptyline/Nortriptyline - Administration of a single oral 50 mg dose of amitriptyline to 15 normal volunteers (10 males and 5 females) who received valproate (500 mg BID) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Rare postmarketing reports of concurrent use of valproate and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Monitoring of amitrptyline levels should be considered for patients taking valproate concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of valproate."

ADVERSE REACTIONS:

Other Patient Populations:

CNS Effects: Addition of "parkinsonism" as last entry to third sentence.

Other: Addition of "Anaphylaxis" as first entry to the subsection.

DOSAGE AND ADMINISTRATION:

General Dosing Advice: New first paragraph -

"Dosing in Elderly Patients - Due to a decrease in unbound clearance of valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced in these patients. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fliud intake and in patients with excessive somnolence. The ultimate therapeutic dose should be acheived on the basis of both tolerabilty and clinical response (see WARNINGS)."

Return to Quick Reference

EFFEXOR XR (venlafaxine HCl) Capsules
[June 12, 2000: Wyeth-Ayerst]

[Other labeling changes not appearing in 2000 PDR: Mar00]

PRECAUTIONS:

General: *Mydriasis*
New subsection -

"Mydriasis has been reported in association with venlafaxine: therefore patients with raised intra-ocular pressure or at risk of acute narrow angle glaucoma should be monitored."

Drug Interactions: Indinavir
New subsection -

"In a study of 9 healthy volunteers, venlafaxine administered under steady-state conditions at 150 mg/day resulted in a 28% decrease in the AUC of a single 800 mg oral dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this finding is unknown.

OVERDOSAGE:

Human Experience: Fourth paragraph deleted -

"In postmarketing experience, there have been reports of fatalities in patients taking overdoses of venlafaxine, predominantly in combination with alcohol and or other drugs."

Replaced with -

"In postmarketing experience, overdose with venlafaxine has occurred predominantly in combination with alcohol and/or other drugs. Electrocardiogram changes (e.g. prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), seizures, vertigo, and death have been reported."

Return to Quick Reference

EVISTA (raloxifene HCl) Tablets
[June 27, 2000: Eli Lilly]

[Other labeling changes not appearing in 2000 PDR: Sep99]

CLINICAL PHARMACOLOGY:

Mechanism of Action: Third paragraph, fourth sentence revised (new text in italics) -

"Raloxifene decreases total and LDL cholesterol levels but does not increase triglyceride levels *(see PRECAUTIONS)*."

PRECAUTIONS:

Lipid Metabolism: New third sentence -

"Limited clinical data suggest that some women with a history of marked hypertriglyceridemia (> 5.6 mmol/L or > 500 mg/dL) in response to treatment with oral estrogen or estrogen plus progestin may develop increased levels of triglycerides when treated with Evista. Women with this medical history should have serum triglycerides monitored when taking Evista."

Patient Package Insert:

What else should I know about Evista?: New sentence added -

"In general, it does not change triglycerides or HDL ("good") cholesterol. However, if you have taken estrogen in the past and had extreme elevations in triglycerides, you should talk with your doctor before taking Evista."

Return to Quick Reference

FOSCAVIR (foscarnet sodium) Injection
[June 13, 2000: Astra]

PRECAUTIONS:

Drug Interactions: Third paragraph revised -

"Abnormal renal function has been reported in connection with the use of Foscavir in combination with ritonavir and/or saquinavir has been observed in clinical practice."

Replaced with revisions incorporated below -

"Abnormal renal function has been observed in clinical practice during the use of Foscavir and ritonavir or Foscavir, ritonavir, and saquinavir. (See DOSAGE and ADMINISTRATION.)"

Geriatric Use: New subsection -

"No studies of the efficacy or safety of Foscavir in persons 65 years of age or older have been conducted. However, Foscavir has been used in patients aged 65 years of age and older. The pattern of adverse events in these patients is consistent across all age groups. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored. (See DOSAGE AND ADMINISTRATION.)"

Return to Quick Reference

GEMZAR (gemcitabine HCl) Injection
[June 23, 2000: Eli Lilly]

ADVERSE REACTIONS:

Single-Agent Use:

Renal - Fourth sentence revised -

"The diagnosis of Hemolytic-Uremic Syndrome (HUS) should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, ["as indicated by" deleted]" elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine or BUN)."

Pulmonary - Subsection revised (new text in italics) -

"Dyspnea was reported in 23% of patients, severe dyspnea in 3%. Dyspnea may be due to underlying disease such as lung cancer (40% of study population) or pulmonary manifestations of other malignancies. Dyspnea was occaisionally accompanied by bronchospasm (<2% of patients). ["Rare reports of prenchymal lung toxicity consistent with drug induced pneumonitis have been associated with the use of Gemzar. Rarely pulmonary edema of unknown etiology, sometimes severe, has occurred in association with Gemzar therapy. Gemzar therapy should be discontinued immediately and appropriate supportive care measures instituted." Deleted] *Pulmonary effects (including pulmonary edema, interstitial pneumonitis, or adult respiratory distress syndrome (ARDS), sometimes severe, have been reported in association with Gemzar therapy. The etiology of these effects is unknown. If such effects develop, Gemzar should be discontinued. Early use of supportive care measures may help ameliorate these conditions.*"

Return to Quick Reference

GENOTROPIN (somatropin) Injection
[June 20, 2000: Pharmacia & Upjohn]

Labeling revised to incorporate information for a new indication - use for the treatment of pediatric patients with Prader-Willi syndrome. Contact the company for a copy of the new labeling/package insert.

Return to Quick Reference

ISMO (isosorbide mononitrate) Tablets
[June 13, 2000: A.H. Robbins]

[Other labeling changes not appearing in 2000 PDR: Jun99]

PRECAUTIONS:

Geriatric Use: New subsection added -

"Clinical studies of Ismo did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, although age, renal, hepatic or cardiac dysfunction do not appear to have a clinically

significant effect on the clearance of Ismo."

Return to Quick Reference

LUVOX (fluvoxamine maleate) Tablets [June 1, 2000: Solvay]

CONTRAINDICATIONS:

First sentence revised (new text in italics) -

"Co-administration of terfenadine, astemizole, cisapride or *pimozide* with Luvox tablets is contraindicated (see WARNINGS and PRECAUTIONS).""

WARNINGS:

Potential Terfenadine, Astemizole, Cisapride and *Pimozide* Interactions Text revised (new text in italics) -

First, second and fifth sentences revised (new text in italics) -

"Terfenadine, astemizole, cisapride and *pimozide* are all metabolized by the cytochrome P450IIIA4 isoenzyme, and it has been demonstrated that ketoconazole, a potent inhibitor of IIIA4, blocks the metabolism of these drugs, resulting in increased plasma concentrations of parent drug. Increased plasma concentrations of terfenadine, astemizole, cisapride and *pimozide* cause QT prolongation and have been associated with torsades de pointes-type ventricular tachycardia, sometimes fatal."

"Consequently, it is recommended that fluvoxamine not be used in combination with either terfenadine, astemizole, cisapride, *and pimozide*. (see CONTRAINDICATIONS and PRECAUTIONS)."

Hyponatremia: New subsection -

"Several cases of hyponatremia have been reported. In cases where the outcome was known, the hyponatremia appeared to be reversible when fluvoxamine was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or with concomitant conditions that might cause hyponatremia. In patients receiving Luvox tablets and suffering from Syndrome of Inappropriate Secretion if Antidiuretic Hormone (SIADH), displacement syndromes, edematous states, adrenal disease or conditions of fluid loss, it is recommended that serum electrolytes, especially sodium as well as BUN and plasma creatinine, be monitored regularly."

Drug Interactions: Last paragraph, first sentence (new text in italics) -

A clinically significant fluvoxamine interaction is possible with drugs having a narrow therapeutic ratio such as terfenadine, astemizole, cisapride *or pimozide*, warfarin, theophylline, certain benzodiazepines and phenytoin."

OVERDOSAGE:

Management of Overdose: Previous subsection significantly revised and is replaced with the following:

"Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

"Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

"Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluvoxamine are known.

"A specific caution involves patients taking, or recently having taken, fluvoxamine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see Tricyclic Antidepressants (TCAs) under Precautions).

"In managing overdosage, consider the possiblity of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physician's Desk Reference (PDR)."

Return to Quick Reference

MELLARIL (thioridazine HCl) Tablets, Oral Suspension & Oral Solution [June 19, 2000: Novartis]

[Other information regarding these changes:Letter]

Labeling extensively revised. Contact the company for a copy of the new labeling/package insert.

Return to Quick Reference

NAVELBINE (vinorelbine) Injection [June 8, 2000: Glaxo Wellcome]

{Other labeling changes not appearing in 2000 PDR: May00]

CLINICAL PHARMACOLOGY:

Pharmacokinetics: New fifth paragraph -

"The influence of age on the pharmacokinetics of vinorelbine was examined using data from 44 cancer patients (average age, 56.7 ± 7.8 years; range, 41 to 74 years; with 12 patients greater than or equal to 60 years and 6 patients greater than or equal to 65 years) in 3 studies. CL (the mean plasma clearance), $t_{1/2}$ (the terminal phase half-life), and V_z (the volume of distribution during terminal phase) were independent of age. A separate pharmacokinetic study was conducted in 10 elderly patients with metastatic breast cancer (age range, 66 to 81 years; 3 patients > 75 years; normal liver function tests) receiving vinorelbine 30 mg/m^2 intravenously. CL, V_{ss}, and $t_{1/2}$ were similar to those reported for younger adult patients in previous studies. No relationship between age, systemic exposure ($AUC_{0\text{-infinity}}$) and hematological toxicity was observed."

PRECAUTIONS:

Geriatric Use: New last sentence -

"The pharmacokinetics of vinorelbine in elderly and younger adult patients are similar (see CLINICAL PHARMACOLOGY)."

Return to Quick Reference

NOLVADEX (tamoxifen citrate) Tablets
[June 29, 2000: AstraZeneca]

Labeling revised to incorporate information on a new indication - use in women with DCIS (Ductal Carcinoma in Situ), following breast surgery and radiation, Nolvadex is indicated to reduce the risk of invasive breast cancer. Contact the company for a copy of the new labeling/package insert.

Return to Quick Reference

NORMOSOL-R (electrolytes & water)
NORMOSOL-R (electrolytes & 5% dextrose)
IONOSOL MB (electrolytes & 5% dextrose)
IONOSOL B (electrolytes & 5% dextrose)
IONOSOL T (electrolytes & 5% dextrose)
Injection

[June 20, 2000: Abbott]

[Other labeling changes not appearing in 2000 PDR: Feb00]

CLINICAL PHARMACOLOGY:

Paragraph describing potassium, third sentence revised (new text in italics) -

"Potassium chloride in water dissociates to provide potassium (K^+) and (Cl^-) ions. Potassium is the chief cation of body cells (160 mEq/liter of intracellular water). It is found in low concentrations in plasma and extracellular fluids (3.5 to 5.0 mEq/liter in a healthy adult *and child over 10 days old; 3.5 to 6.0 mEq/liter in a child less than 10 days old.*)"

Paragraph describing water as an essential body constituent followed by a new table -

"Water is an essential constituent of all body tissues and accounts for approximately 70% of total body weight. Average normal adult daily requirement ranges from two to three liters (1.0 to 1.5 liters each for insensible water loss by perspiration and urine production)."

New text and table -

"Average normal pediatric daily requirements are based on the child's weight as described in the table below:

Weight	Fluid Requirements
Up to 10 kg	100 mL/kg
11 to 20 kg	1,000 mL + 50 mL/kg for each kg above 10 kg
Above 20 kg	1,500 mL + 20 mL/kg for each kg above 20 kg

WARNINGS:

Two new paragraphs added [Normosol-R, all formulations, June 15, 2000] -

"Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function during fluid replacement with Normosol-R [Normosol-R and Dextrose]."

"Elderly patients may be at increased risk for the development of fluid overloading and dilutional hyponatremia following Normosol-R [Normosol-R and Dextrose] administration."

PRECAUTIONS:

Pediatric Use: New subsection [dextrose containing formulations] -

"The safety and effectiveness in the pediatric population are based on the similarity of the clinical conditions of the pediatric and adult populations. In neonates or very small infants the volume of fluid may affect fluid and electrolyte balance.

"Frequent monitoring of serum glucose concentrations is required when dextrose is prescribed to pediatric patients, particularly neonates and low birth weight infants.

"In very low birth weight infants, excessive or rapid administration of dextrose injection may

result in increased serum osmolality and possible intracerebral hemorrhage. "

New subsection [Normosol-R and water formulation] -

"The safety and effectiveness of Normosol-R have been established in the age groups of birth to 16 years. Use of Normosol-R is supported by evidence from adequate and well-controlled clinical studies in adults with additional data from post-marketing experience in the pediatric population."

Geriatric Use: [Normosol -R, all formulations, June 15, 2000]
New subsection -

"Clinical studies of Normosol -R did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

"Elderly patients have been shown to secrete higher levels of antidiuretic hormone than younger patients, which may increase the risk of fluid overloading, and dilutional hyponatremia in these patients. See WARNINGS.

"This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. See WARNINGS."

DOSAGE AND ADMINISTRATION:
[products containing dextrose] New second paragraph -

"As reported in the literature, the dosage and constant infusion rate of intravenous dextrose must be selected with caution in pediatric patients, particularly neonates and low birth weight infants, because of the increased risk of hyperglycemia/hypoglycemia. "

INSTRUCTIONS FOR USE:
Preparation for Administration: Steps 1 through 8 (Steps 1 through 9 for Normosol -R) deleted.

Replaced by new subsection:

To Administer

"1. Attach administration set per manufacturer's instructions."
"2. Regulate rate of administration per institutional policy."

INSTRUCTIONS FOR USE:
[Normosol -R & 5% dextrose] New paragraph -

"Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety."

Return to Quick Reference

ORTHO-CYCLEN
ORTHO-TRI-CYCLEN
(norgestimate/ethinyl estradiol)
Tablets

[June 5, 2000: R.W. Johnson]

DETAILED PATIENT LABELING:

Effectiveness Of Oral Contraceptives For Contraception: Text revised (new text in italics) -

"In comparison, typical failure rates for other non-surgical methods of birth control during the first year of use are as follows:

Implant: <1%
Injection: <1%
IUD: 1 to 2%
Diaphragm with spermicides: ["18%" deleted] *20%*
Spermicides alone: ["21%" deleted]*26%,*
Vaginal sponge: ["18 to 36%" deleted] *20 to 40%*
Female sterilization: <1%
Male sterilization: <1%
Cervical Cap *with spermicides*: ["18 to 36%" deleted] *20 to 40%*
Condom alone (male): ["12%" deleted] *14%*
Condom alone (female): 21%
Periodic abstinence: ["20%" deleted] *25%*
Withdrawal: 19%
No Methods: 85% "

Return to Quick Reference

ORTHO-NOVUM 1/50 (norethindrone/mestranol) Tablets
[June 5, 2000: R.W. Johnson]

[Note: These changes appear in the 2000 PDR]

INDICATIONS AND USAGE:

"Table 1: PERCENTAGE OF WOMEN EXPERIENCING AN UNINTENDED PREGNANCY DURING THE FIRST YEAR OF TYPICAL USE AND THE FIRST YEAR OF PERFECT USE OF CONTRACEPTION AND THE PERCENTAGE CONTINUING USE AT THE END OF THE FIRST YEAR. UNITED STATES" (Trussel table) and reference no.1 has been updated from 1994 to 1998. (Contact the company for a copy of the new labeling/package insert)

WARNING:

3. CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS: Second paragraph, also found in the corresponding paragraph in DETAILED PATIENT LABELING,

"Cancer of the reproductive organs and breasts" -

"A meta-analysis of 54 studies reports that women who are currently using combined oral contraceptives or have used them in the past 10 years are at a slightly increased risk of having breast cancer diagnosed although the additional cancers tend to be localized to the breast. There is no evidence of an increased risk of having breast cancer diagnosed 10 or more years after the cessation of use."

has been revised. The revised paragraph reads:

"A meta-analysis of 54 studies found a small increase in the frequency of having breast cancer diagnosed for women who were currently using combined oral contraceptives or had used them in the past 10 years. This increase in the frequency of breast cancer diagnosis, within 10 years of stopping use, was generally accounted for by cancers localized to the breast. There was no increase in the frequency of having breast cancer diagnosed ten or more years after cessation of use."

Third paragraph, first sentence revised (new text in italics) -

"Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical *intraepithelial* neoplasia in some populations of women."

PRECAUTIONS:

Nursing Mothers: Second and third sentences revised (new text in italics) Also found in the corresponding text of the DETAILED PATIENT LABELING, "GENERAL PRECAUTIONS, 2. While breast feeding" section (fourth and fifth sentences) -

"In addition, *combination* oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use *combination* oral contraceptives but to use other forms of contraception until she has completely weaned her child."

Pediatric Use: New subsection -

"Safety and efficacy of ORTHO-NOVUM 1/50 Tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated."

Return to Quick Reference

PRAVACHOL (pravastatin sodium) Tablets [June 23, 2000: Bristol-Myers Squibb]

[Other labeling changes not appearing in 2000 PDR: Jan00, Feb00]

CLINICAL PHARMACOLOGY:

Pharmacokinetics/Metabolism: New last paragraph -

"In a single oral dose study using pravastatin 20 mg, the mean AUC for pravastatin was approximately 27% greater and the mean cumulative urinary excretion (CUE) approximately 19% lower in elderly men (65-75 years old) compared with younger men (19 to 31 years old). In a similar study conducted in women, the mean AUC for pravastatin was approximately 46% higher and the mean CUE approximately 18% lower in elderly women (65 to 78 years old) compared to younger women (18 to 38 years old). In both studies C_{max}, T_{max} and $T_{1/2}$ values were similar in older and younger subjects."

Clinical Studies: New last sentence in first paragraph regarding the Pravastatin Primary Prevention Study (West of Scotland Coronary Prevention Study - WOS) -

"Median (25^{th}, 75^{th} percentile) percent changes from baseline after 6 months of pravastatin treatment in Total C, LDL-C, TG, and HDL were - 20.3 (-26.9, -11.7), -27.7 (-36.0, -16.9), -9.1 (-27.6, 12.5), and 6.7 (-2.1, 15.6), respectively."

New fourth sentence in the paragraph regarding the Cholesterol and Recurrent Events (CARE) study -

"Median (25^{th}, 75^{th} percentile) percent changes from baseline after 6 months of pravastatin treatment in Total C, LDL-C, TG, and HDL were -22.0 (-28.4, -14.9), -32.4 (-39.9, -23.7), -11.0 (-26.5, 8.6), and 5.1 (-2.9, 12.7), respectively."

Primary Hypercholesterolemia (Fredrickson Type IIa and IIb)
Second paragraph, first sentence revised -

"A single daily dose ["administered in the evening (the recommended dosing)" deleted] is as effective as the same total daily dose given twice a day."

INDICATIONS AND USAGE:

Hyperlipidemia: Subsection previously named "Hypercholesterolemia and Mixed Dyslipidemia"
First paragraph revised (new text in italics) -

"Pravachol is indicated as an adjunct to diet to reduce elevated Total-C, Apo B, and TG levels *and to increase HDL-C* in patients with primary hypercholesterolemia and mixed dyslipidemia (Frederickson Type IIa and IIb)."

PRECAUTIONS:

Geriatric Use: New subsection -

"Two secondary prevention trials with pravastatin (CARE and LIPID) included a total of 6,593 subjects treated with pravastatin 40 mg for periods ranging up to 6 years. Across these two studies, 36.1% of pravastatin subjects were 65 and older and 0.8% were aged 75 and older. The beneficial effect of pravastatin in elderly subjects in reducing cardiovascular events and in modifying lipid profiles was similar to that seen in younger subjects. The adverse event profile in the elderly was similar to that in the overall population. Other reported clinical experience has not identified differences to pravastatin between elderly and younger patients.

Mean pravastatin AUCs are slightly (25-50%) higher in healthy elderly subjects than in healthy younger subjects, but mean C_{max}, T_{max} and $T_{1/2}$ values are similar in both age groups and substantial accumulation of pravastatin would not be expected in the elderly (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism)."

ADVERSE REACTIONS:

first paragraph, last sentence revised (new text in italics) -

"["During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients." Deleted] *(See also PRECAUTIONS: Geriatric Use section)* "

Return to Quick Reference

PREVACID (lansoprazole) Capsules
[June 20, 2000: TAP Pharmaceuticals]

[Other labeling changes not appearing in 2000 PDR: Jan99]

ADVERSE REACTIONS:

Clinical: Fifth paragraph revised (new text in italics) -

"Additional adverse experiences occurring in <1% of patients or subjects in domestic ["and/or international" deleted] trials [", or occurring since the drug was marketed," deleted] are shown below ["within each body system" deleted]. *Refer to **Postmarketing** for adverse reactions occurring since the drug was marketed.*

Body as a Whole - "anaphylactoid-like reaction" moved to Postmarketing
Digestive System - "vomiting" moved to Postmarketing
Hematologic and Lymphatic System - renamed *Hemic and Lymphatic System* - "agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia and thrombotic thrombocytopenic purpura" moved to Postmarketing."
Urogenital system - "urinary retention" moved to Postmarketing

["The majority of hematologic cases received were foreign-sourced and their relationship to lansoprazole was unclear" deleted]

Postmarketing: new subsection -

On-going Safety Surveillance: Additional adverse experiences have been reported since lansoprazole has been marketed. The majority of these cases are foreign-sourced and a relationship to lansoprazole has not been established. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events are listed below by COSTART body system.

Body as a Whole - anaphylactoid-like reaction; Digestive System - hepatotoxicity, vomiting; Hemic and Lymphatic System - agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia,

neutropenia, pancytopenia, thrombocytopenia and thrombotic thrombocytopenic purpura; Special Senses - speech disorder; Urogenital System - urinary retention.

Return to Quick Reference

QUINAGLUTE DURA-TABS (quinidine gluconate) Tablets
[June 24, 2000: Berlex]

[Note: These changes appear in 2000 the PDR]

CLINICAL PHARMACOLOGY:

Pharmacokinetics and Metabolism: First paragraph, new last sentence -

"The rate of absorption of quinidine following the ingestion of grapefruit juice may be decreased."

PRECAUTIONS:

Drug *and Diet* Interactions: (Previously " Drug Interactions")
Altered pharmacokinetics of quinidine: two interactions added to end of subsection -

"Grapefruit juice: Grapefruit juice inhibits P450 3A4-mediated metabolism of quinidine to 3-hydroxyquinidine. Although the clinical significance of the interaction is unknown, grapefruit juice should be avoided.

"Dietary salt: The rate and extent of quinidine absorption may be affected by changes in dietary salt intake; a decrease in dietary salt intake may lead to an increase in plasma quinidine concentrations."

Non-interactions of quinidine with other drugs: Second paragraph, first sentence revised -

"Conversely, the pharmacokinetics of quinidine are not significantly affected by caffeine, ciprofloxacin, digoxin, ["diltiazem" deleted], felodipine, omeprazole, or quinine.

OVERDOSAGE:

Accelerated removal:: Last paragraph revised (new text in italics) -

"Following quinidine overdose, drugs that delay elimination of quinidine (cimetidine, carbonic-anhydrase inhibitors, *diltiazem*, thiazide diuretics) should be withdrawn unless absolutely required."

Return to Quick Reference

REGLAN (metoclopramide) Tablets, Injection & Syrup
[June 1, 2000: Wyeth-Ayerst]

ADVERSE REACTIONS: Hematologic: Addition of "Sulfhemoglobinemia in adults". Substantial

additions regarding pediatric patients to the **CLINICAL PHARMACOLOGY, Pharmacokinetics** subsection and **PRECAUTIONS, Pediatric Use** subsection. Contact the company for a copy of the new labeling/package insert.

Return to Quick Reference

RHINOCORT (budesonide) Nasal Inhaler [June 2, 2000: AstraZeneca]

PRECAUTIONS:

Geriatric Use: New subsection -

"Clinical studies of Rhinocort Nasal Inhaler did not include a sufficient number of patients 65 years of age and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in either clinical safety or efficacy between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy."

Return to Quick Reference

SEREVENT (salmeterol xinafoate) Inhalation Aerosol & Diskus [June 29, 2000: Glaxo]

CLINICAL PHARMACOLOGY:

Effects in Patients with Asthma on Concomitant Inhaled Corticosteroids: New subsection provides information on use with inhaled corticosteroids -

"In 4 clinical trials in adult and adolescent patients with asthma (n = 1922), the effect of adding salmeterol to inhaled corticosteroid therapy was evaluated. The studies utilized the inhalation aerosol formulation of salmeterol xinafoate for a treatment period of 6 months. They compared the addition of salmeterol therapy to an increase (at least doubling) of the inhaled corticosteroid dose.

"Two randomized, double-blind, parallel group clinical trials (n = 997) enrolled patients (ages 18 - 82 years) with persistent asthma who were previously maintained but not adequately controlled on inhaled corticosteroid therapy. During the 2-week run-in period, all patients were switched to beclomethasone dipropionate 168 mcg twice daily. Patients still not adequately controlled were randomized to either the addition of salmeterol inhalation aerosol 42 mcg twice daily or an increase of beclomethasone dipropionate to 336 mcg twice daily. As compared to the doubled dose of beclomethasone dipropionate, the addition of salmeterol resulted in statistically significantly greater improvements in pulmonary function and asthma symptoms, and statistically significantly greater reduction in supplemental albuterol use. The percent of patients who experienced asthma exacerbations overall was not different between groups (i.e., 16.2% in the salmeterol group versus 17.9% in the higher dose beclomethasone dipropionate group).

"Two randomized, double-blind, parallel group clinical trials (n = 925) enrolled patients (ages 12 - 78 years) with persistent asthma who were previously maintained but not adequately controlled on prior therapy. During the 2 - 4 week run-in period, all patients were switched to fluticasone propionate 88 mcg twice daily. Patients still not adequately controlled were randomized to either the addition of salmeterol inhalation aerosol 42 mcg twice daily or an increase of fluticasone propionate to 220 mcg twice daily. As compared to the increased (2.5 times) dose of fluticasone propionate, the addition of salmeterol resulted in statistically significantly greater improvements in pulmonary function and asthma symptoms, and statistically significantly greater reduction in supplemental albuterol use. Fewer patients receiving salmeterol experienced asthma exacerbations than those receiving the higher dose of fluticasone propionate (8.8% versus 13.8%)."

Return to Quick Reference

SERZONE (nefazodone) Tablets
[June 1, 2000: Bristol-Myers Squibb]

CONTRAINDICATIONS, WARNINGS, PRECAUTIONS:

[Note: These changes appear in the 2000 PDR]

"pimozide" is included with "terfenidine, astemizole, cisapride" regarding interactions.

PRECAUTIONS:

Drug Interactions: [Not appearing in 1999 PDR; extensively revised in the 2000 PDR] Revisions incorporated in the following paragraph -

"There have been reports of increased blood concentrations of cyclosporine and tacrolimus into toxic ranges when patients received these drugs concomitantly with Serzone. Both cyclosporine and tacrolimus are substrates of CYP3A4, and nefazodone is known to inhibit this enzyme. If either cyclosporine or tacrolimus is administered with Serzone, blood concentrations of the immunosuppressive agent should be monitored and dosage adjusted accordingly."

ADVERSE REACTIONS:

Postintroduction Clinical Experience: [Appearing in 2000 PDR] New last sentence (paragraph) -

"Rare reports of liver necrosis and liver failure, in some cases leading to liver transplantation and/or death."

OVERDOSAGE:

Human Experience: [For 1999 PDR only] First sentence deleted -

"There is very limited experience with nefazodone overdose."

Overdose Management [Extensive revisions to the 1999 PDR subsection] Revisions incorporated in the following paragraphs:

"Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

"Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

"Activated charcoal should be administered. Due to the wide distribution of nefazodone in body tissues, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for nefazodone are known.

"In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physician's Desk Reference."

Return to Quick Reference

SODIUM ACETATE Injection
[June 15, 2000: Abbott]

PRECAUTIONS:

Geriatric Use: New subsection -

"An evaluation of current literature revealed no clinical experience identifying differences in response between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

"Sodium (and potassium) ions are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function."

Return to Quick Reference

SODIUM PHOSPHATES Injection
[June 16, 2000: Abbott]

PRECAUTIONS:

Geriatric Use: New subsection -

"An evaluation of current literature revealed no clinical experience identifying differences in response between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater

frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

"Sodium ions and phosphorus ions are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function."

Return to Quick Reference

STERILE WATER Injection
[June 14, 2000: Abbott]

PRECAUTIONS:

Pediatric Use: Revisions incorporated in paragraph below -

"The safety and effectiveness in the pediatric population are based on the similarity of the clinical conditions of the pediatric and adult populations. In neonates or very small infants the volume of fluid may affect fluid and electrolyte balance."

Return to Quick Reference

TAXOL (paclitaxel) Injection
[June 20, 2000: Bristol-Myers Squibb]

[Other labeling changes not appearing in 2000 PDR: Oct99, Dec99]

Labeling provides for use as a 3-hour infusion of Taxol (paclitaxel) Injection given every 3 weeks at a dose of 175 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2 for the first-line treatment of advanced ovarian cancer. Contact the company for a copy of the new labeling/package insert.

Return to Quick Reference

TICLID (ticlopidine) Tablets
[June 14, 2000: Hoffmann-La Roche]

BOXED WARNING:

First paragraph revised (new text in italics) -

"WARNING: Ticlid can cause life-threatening hematological adverse reactions, including neutropenia/agranulocytosis, ["and" deleted] thrombocytopenia purpura (TTP) *and aplastic anemia.*"

New fourth paragraph -

" *Aplastic Anemia*: Aplastic anemia was not seen during clinical trials, but US physicians reported about 50 cases between 1992 and 1998. Based on an estimated patient exposure of 2 million to 4 million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine-associated aplastic anemia may be as high as one case in every 4000 to 8000 patients exposed."

Fifth paragraph (new text in italics) -

"Monitoring of Clinical and Hematologic Status: Severe hematological adverse reactions may occur within a few days of the start of therapy. The incidence of TTP peaks after about 3 to 4 weeks of therapy and neutropenia peaks at approximately 4 to 6 weeks ["with both declining thereafter" deleted]. *The incidence of aplastic anemia peaks after about 4 to 8 weeks of therapy. The incidence of the hematologic adverse reactions declines thereafter.* Only a few cases *of neutropenia, TTP, or aplastic anemia* have arisen after more than 3 months of ["treatment" deleted] *therapy*."

INDICATIONS AND USAGE:

Second paragraph (new text in italics) -

"Because Ticlid is associated with a risk of life-threatening blood dyscrasias including thrombotic thrombocytopenic purpura (TTP),["and" deleted] neutropenai/agranolocytosis *and aplastic anemia* (see BOXED WARNING and WARNINGS), Ticlid should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy."

CONTRAINDICATIONS:

Second bullet revised (new text in italics) -

"• Presence of hematopoietic disorders such as neutropenia and thrombocytopenia or a past history of *either* TTP *or aplastic anemia*"

WARNINGS:

Hematological Adverse Reactions: Second sentence revised (new text in italics) -

"Bone-marrow examination typically shows a reduction in ["myeloid" deleted] *white blood cell* precursors."

Aplastic Anemia: New subsection -

"Aplastic anemia is characterized by anemia, thrombocytopenia and neutropenia together with a bone marrow examination that shows decreases in the precursor cells for red blood cells, white blood cells, and platelets. Patients may present with signs or symptoms suggestive of infection, in association with low white blood cell and platelet counts. **Prompt** treatment, which may include the use of drugs to stimulate the bone marrow, can minimize the mortality associated with aplastic anemia."

Monitoring for Hematologic Adverse Reactions: Second paragraph, first sentence revised (new text in italics) -

"Clinically, fever might suggest ["either" deleted] neutropenia, ["or" deleted], TTP, *or aplastic anemia*; TTP might also be suggested by weakness, pallor, petechiae or purpura, dark urine (due to blood, bile pigments, or hemoglobin) or jaundice, or neurological changes."

Third paragraph; second, fifth sentences revised (new text in italics), new fourth sentence (in italics) -

"Ticlopidine is occasionally associated with thrombocytopenia unrelated to TTP *or aplastic anemia*."

" *A simultaneous decrease in platelet count and WBC count should prompt further investigation for a diagnosis of aplastic anemia.* "

"If there are laboratory signs of TTP, or if the neutrophil count is confirmed to be < $1200/mm^3$, then ["the drug" deleted] *Ticlid* should be discontinued *immediately*."

Other Hematological Effects: First sentence revised (new text in italics) -

"Rare cases of agranulocytosis, pancytopenia, or ["aplastic anemia" deleted] *leukemia* have been reported in postmarketing experience, some of which have been fatal."

PRECAUTIONS:

Laboratory Tests: *Liver Function*: First sentence revised (new text in italics) -

"Ticlid therapy has been associated with elevations of alkaline phosphatase, *bilirubin*, and transaminases, which generally occurred within 1 to 4 months of therapy initiation."

Second paragraph revised (new text in italics) -

Postmarketing experience includes rare individuals with elevations in their transaminases and bilirubin to > 10X above the upper limits of normal. Based on postmarketing and clinical trial experience, liver function testing, including ["SGPT and GGTP" deleted] *ALT, AST, and GGT*, should be considered whenever liver dysfunction is suspected, particularly during the first 4 months of treatment."

ADVERSE REACTIONS:

Hematological: (new text in italics) -

"Neutropenia/thrombocytopenia, TTP, *aplastic anemia* , (see BOXED WARNING and WARNINGS), *leukemia*, agranulocytosis, eosinophilia, pancytopenia, thrombocytosis and bone-marrow depression have been reported."

Less Frequent Adverse Reactions (Probably Related): Paragraph at end of subsection revised (new text in italics)-

"In addition, rarer, relatively serious *and potentially fatal* events *associated with the use of Ticlid* have also been reported from postmarketing experience: Hemolytic anemia with reticulocytosis, ["aplastic anemia" deleted], immune thrombocytopenia, hepatitis, hepatocellular jaundice, cholestatic jaundice, hepatic necrosis, *hepatic failure,* peptic ulcer, renal failure, nephrotic syndrome, hyponatremia, vasculitis, sepsis, *allergic reactions (including* angioedema, allergic

pneumonitis, *and anaphylaxis)*, systemic lupus (positive ANA), peripheral neuropathy, serum sickness, arthropathy and myositis."

IMPORTANT INFORMATION ABOUT TICLID (ticlopidine HCl) TABLETS:

Special Warning for Users of TICLID/Necessary Blood Tests:
Two new paragraphs added to end of subsection -

"Rarely, decreases in the white blood cells, red blood cells and platelets can occur together. This condition is called aplastic anemia and can be fatal.

"Things you should watch for as possible early signs of aplastic anemia are feeling of excessive weakness and tiredness, paleness, bruising, and bleeding from areas such as your nose or gums. You may also develop signs of infection such as fever. If any of these occur, contact your doctor immediately."

Other Warnings and Precautions: Second paragraph (new text in italics) -

"If any of the symptoms described above for neutropenia, TTP, *aplastic anemia* or jaundice occur, contact your doctor immediately."

Return to Quick Reference

TONOCARD (tocainide HCl) Tablets
[June 2, 2000: Astra]

HOW SUPPLIED:

Storage: Text deleted -

"Store below 40°C (104°F), preferably between 15°C and 30°C (59°F and 86°F). Store in a well-closed container."

Replaced with -

"Store at 25°C (77°F): excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed."

Return to Quick Reference

UREAPHIL (sterile urea) Injection
[June 6, 2000: Abbott]

PRECAUTIONS:

Geriatric Use: New subsection -

KLOTZ DEPOSITION EXHIBIT 30

D'S EXHIBIT H

Eur J Clin Pharmacol (2000) 56: 1–18

REVIEW ARTICLE

Klotz
EXHIBIT NO. 30
5-16-07
MICHELLE KEEGAN

F. De Ponti · E. Poluzzi · N. Montanaro

QT-interval prolongation by non-cardiac drugs: lessons to be learned from recent experience

Received: 4 October 1999 / Accepted in revised form: 13 January 2000

Abstract *Background*: Evidence has accrued that several non-cardiac drugs may prolong cardiac repolarisation (hence, the QT interval of the surface electrocardiogram) to such a degree that potentially life-threatening ventricular arrhythmias (e.g. torsades de pointes) may occur, especially in case of overdosage or pharmacokinetic interactions.
Discussion: This has fostered discussion on the molecular mechanisms underlying the class-III antiarrhythmic effect shared by apparently disparate classes of drugs, on the clinical relevance of this side effect and on possible guidelines to be followed by drug companies, ethics committees and regulatory agencies in the risk–benefit assessment of new and licensed drugs. This review provides an update on the different classes of non-cardiac drugs reported to prolong the QT interval (e.g. histamine H_1-receptor antagonists, antipsychotics, antidepressants and macrolides), on the possible underlying molecular mechanisms and on the clinical relevance of the QT prolonging effect. Identification and widespread knowledge of risk factors that may precipitate prolongation of the QT interval into life-threatening arrhythmias becomes an important issue. Risk factors include congenital long QT syndrome, clinically significant bradycardia or heart disease, electrolyte imbalance (especially hypokalaemia, hypomagnesaemia), impaired hepatic/renal function and concomitant treatment with other drugs with known potential for pharmacokinetic/pharmacodynamic interactions (e.g. azole antifungals, macrolide antibacterials and class-I or -III antiarrhythmic agents). Future perspectives for drug research and development are also briefly outlined.

F. De Ponti (✉) · E. Poluzzi · N. Montanaro
Department of Pharmacology,
University of Bologna and Interuniversity Research Centre for Pharmacoepidemiology, Via Irnerio 48,
I-40126 Bologna BO, Italy
e-mail: deponti@biocfarm.unibo.it
Tel.: +39-051-2091805; Fax: +39-051-248862

Key words Adverse drug reactions · QT interval · Cardiac arrhythmias

Introduction

Since the mid 1980s, evidence has accrued that several classes of non-cardiac drugs may significantly prolong the QT interval of the surface electrocardiogram (ECG) and have cardiotoxic potential (risk of life-threatening arrhythmias). In the 1960s and 1970s, reports already existed on the cardiotoxicity of some drug classes, such as anti-psychotics and first-generation histamine H_1-receptor antagonists (for references, see Zhang [1] and Kitayama et al. [2]), but these remained mostly confined to the specialised literature, and the ability of non-cardiac drugs to prolong the QT interval was usually considered as a pharmacological "curiosity" of uncertain clinical significance and the molecular mechanisms remained obscure.

Several reasons have fuelled interest on the QT-prolonging potential of non-cardiac drugs. Firstly, drug-induced lengthening of the QT interval (stemming from a drug's ability to prolong the cardiac action potential duration) has been associated with the occurrence of ventricular tachyarrhythmias, namely *torsades de pointes*, a polymorphous ventricular arrhythmia that may cause syncope and degenerate into ventricular fibrillation [3]. Secondly, there is an ongoing debate in the literature [4] on the clinical significance of a prolonged QT interval, which has been found to be a risk factor for sudden death due to cardiac arrest [5] and also for all-cause mortality [6, 7]. Thirdly, several apparently chemically unrelated classes of drugs have been implicated in prolongation of the QT interval, and pharmacologists have been challenged by the question whether this is a class effect (e.g. shared by all agents of a given pharmacological class such as antihistamines) or a specific effect of a few agents within a pharmacological class. Finally, several interventions by regulatory agencies and/or drug companies (Table 1) have fostered

Table 1 Examples of interventions on non-cardiac drugs with QT prolonging potential

	USA	Europe
Terodiline	–	Withdrawn after reports of cases of torsades de pointes (1991)
Terfenadine	Proposal to withdraw (January 1997)[a] Drug labelling changes: new warnings (September 1997)[b] Withdrawn after approval of fexofenadine (December 1997)[c]	120-mg Tablets withdrawn from EU market (November 1997)[d] 60-mg and 30-mg tablets and 6-mg/ml oral suspension maintained (February 1998)[e]
Cisapride	Drug labelling change: new warnings (1998)[f]	Drug labelling change: new warnings (1998)[g]
Sertindole	Recommended for approval, but not licensed (1996)[h]	Precautionally withdrawn from EU market pending EMEA judgement (1998)[i]
Astemizole	Withdrawn by the manufacturer (1999)	Withdrawn by the manufacturer (1999)
Grepafloxacin	Withdrawn by the manufacturer (1999)	Withdrawn by the manufacturer (1999)

[a] http://www.fda.gov/medwatch/safety/1997/seldan.htm
[b] http://www.fda.gov/bbs/topics/ANSWERS/ANS00823.html
[c] http://www.fda.gov/bbs/topics/ANSWERS/ANS00843.html
[d] http://www.eudra.org/humandocs/PDFs/PhV/EN/100097en.pdf
[e] http://www.eudra.org/humandocs/PDFs/PhV/EN/025598en.pdf; http://www.eudra.org/humandocs/PDFs/PhV/EN/025698en.pdf; http://www.eudra.org/humandocs/PDFs/PhV/EN/025798en.pdf
[f] http://www.fda.gov/medwatch/safety/1998/propul.htm
[g] http://www.imb.ie/pubs/drugnews/news8.pdf
[h] http://www.fda.gov/oc/oms/ofm/budget/fooddrugstat.htm; http://www.fda.gov/cder/da/da1096.htm
[i] http://www.open.gov.uk/mca/csm/serdolect.htm

discussion on the impact of QT-prolonging effects on drug development and on whether a more carefully focussed drug-development program could have prevented some of the reported fatal adverse reaction. This dilemma is not easily solved, since, although prolongation of the QT interval by non-cardiac drugs is not an unusual finding, potentially fatal arrhythmias, such as torsades de pointes, are uncommon and are unlikely to occur during the course of phase I–III studies, when relatively small numbers of subjects are exposed to the investigational drug. However, when we analyse some of the initial case reports of drug-induced life-threatening arrhythmias with hindsight, it is clear that several of these adverse reactions would have been preventable, had the potential for pharmacokinetic interactions (e.g. with CYP3A4 isoenzyme inhibitors) been known at that time.

The aim of this review is to provide an updated overview of different classes of compounds that are not intended for cardiac use and have been reported to prolong the QT interval, to outline possible pharmacodynamic/pharmacokinetic mechanisms and to consider this information from a clinical and regulatory perspective.

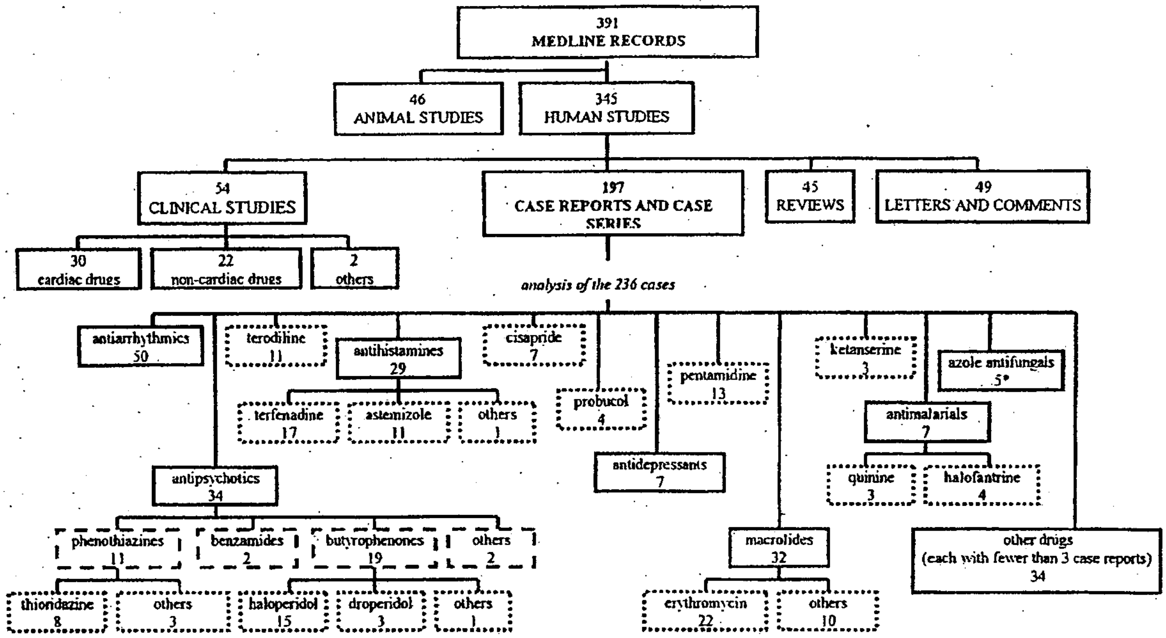
Classes of drugs and mechanisms underlying QT prolongation

Through a Medline search for literature published from 1985 through 1998 using the MESH terms "long-QT syndrome – chemically induced" or "torsades-de-pointes – chemically induced", we retrieved 391 records. This approach was used as a starting point to obtain an overview of the drugs associated with a prolonged QT interval (Fig. 1), although it certainly underestimates the real number of publications dealing with drug-induced prolongation of the QT interval. The 391 Medline records were classified as indicated in Fig. 1, and the 197 case reports/case series (for a total number of 236 cases) were analysed by identifying the drugs/drug classes associated with prolongation of the QT interval/occurrence of torsades de pointes. Apart from anti-arrhythmics, the largest numbers of cases within single classes refer to anti-psychotics, histamine H_1-receptor antagonists and macrolides.

With such a diverse spectrum of molecules, the pharmacologist is challenged by questions on the molecular mechanism(s) underlying prolongation of the QT interval by apparently unrelated molecules. Table 2 provides a synopsis of different classes of drugs with QT-prolonging potential and possible mechanisms of class-III anti-arrhythmic action.

Since the QT interval is the summation of the duration of ventricular depolarisation and repolarisation, it is thought to reflect individual action potential duration in cardiac myocytes. Cardiac action potential duration is in turn controlled by a delicate balance between inward and outward currents in the plateau repolarisation phase. Since outward K^+ currents, especially the delayed rectifier repolarising current, I_K (which is the sum of two kinetically and pharmacologically distinct types of K^+ currents: a rapid I_{Kr} and a slow I_{Ks} component), are thought to play an important role during plateau repolarisation and in determining the configuration of the action potential, small changes in conductance can significantly alter the effective refractory period, hence the action potential duration.

Several studies support the notion that the basic mechanism by which most of the drugs listed in Table 2 prolong the QT interval can be related to blockade of potassium currents. Drugs such as amiodarone and d-sotalol exert their class-III anti-arrhythmic properties through this mechanism. In particular, d-sotalol fully blocks the rapid component of I_K (I_{Kr}) at concentrations that have no effect on I_{Ks}. Several of the drugs



*all cases involved an association with H_1-receptor antagonists

Fig. 1 Records obtained through a Medline search for literature published from 1985 to 1998, using the MESH terms "long-QT-syndrome – chemically-induced" or "torsades-de-pointes – chemically induced". The search retrieved 391 records: 345 refer to humans and 197 are case reports or case series. The latter include a total number of 236 cases, which were analysed by identifying the compounds associated with prolongation of the QT interval/occurrence of torsades de pointes. *Numbers* below a drug/drug class refer to the number of the reported cases

reported to significantly prolong the QT interval in a clinical setting (such as terfenadine, astemizole and i.v. macrolides) were shown to inhibit the rapid component of the delayed rectifier K^+ current (I_{Kr}) in electrophysiological studies and to block potassium channels encoded by the human ether-à-go-go-related gene (HERG) (see Table 2 and Table 3 for references). Although I_{Kr} is the most extensively studied, action on other potassium currents (e.g. the transient outward current I_{to}, the ultrarapidly activating delayed rectifier current I_{Kur} and the inward rectifier I_{K1} current) may account for a prolongation of the action potential duration. Several reviews on cardiac potassium channels and on gene(s)/gene product(s) thought to be responsible for a given current are available [8, 9, 10]. At present, the role of different currents in shaping the cardiac action potential in health and disease is a matter of extensive investigations, and the clinical application of basic knowledge on ionic currents is still in its infancy. The overall relevance of a given current may depend on the type of ion channels expressed in different parts of the heart (e.g. atrium vs ventricle), on the species and on the pathophysiological condition (low vs high heart rate; ischaemic vs normal myocardium).

Structure–activity relationships for QT-prolonging effect

It may seem surprising that, at present, our knowledge on structure–activity relationships for class-III anti-arrhythmic activity is still rather fragmentary. This stems in part from the fact that class-III activity of a compound was traditionally evaluated by assessing the prolongation of the action potential duration (e.g. at 50% and 90% of repolarisation, referred to as APD_{50} and APD_{90}, respectively), an approach that does not take into due account the possible contribution of different currents during repolarisation and therefore may classify drugs with pharmacologically distinct properties as belonging to the same group.

A few years ago, Morgan and Sullivan [11] published one of the most extensive reviews on structure–activity relationships for class-III anti-arrhythmic drugs and proposed the structural requirements for a class-III pharmacophore (Fig. 2): a *para*-substituted phenyl ring connected to a basic nitrogen via a highly variable linking chain. From a quick overview of the molecular structures of the compounds reported to prolong the QT interval and block HERG K^+ channels, it emerges that some molecules (e.g. terfenadine and astemizole) indeed satisfy the criteria to display class-III properties, whereas the class-III pharmacophore proposed by Morgan and Sullivan is not easily identifiable in other compounds (e.g. probucol and erythromycin). Of course, the possibility remains that a closer analysis might reveal that, in some cases, metabolites and not the parent compound are responsible for class-III

Table 2 Classes of drugs with QT-prolonging potential and possible mechanism(s) of action[a]

	Dose associated with QTc increase (ΔQTc recorded)[b]	Population	Reference	Possible mechanism(s) of action and additional information	Reference
Anti-psychotics					
Anti-psychotic medication	Long-term conventional doses (mean QTc 447 vs 417, treated vs untreated patients)	Patients with schizophrenia without cardiac disease	[2]	Prolonged QTc interval and QTc dispersion not associated with increased risk of ventricular tachyarrhythmia	[2]
	> 4-week treatment with > 2,000 mg chlorpromazine equivalents daily (odd ratio for prolonged QTc interval = 4.28)	In-patients	[36]	Several anti-psychotics exert class-III anti-arrhythmic effects at micromolar concentrations in vitro	[37, 38]
Thioridazine	50-mg single oral dose (22 ms)	Healthy volunteers	[39]		
	500 mg	Overdosage	[40]		
Chlorpromazine	100 mg daily	Case report	[41]		
Haloperidol	4 mg per os	Case report	[42]	Inhibition of HERG K^+ channels (both haloperidol and its reduced metabolite)	[48]
	50 mg per os daily	Case report	[43]		
	> 50 mg i.v. (haloperidol or droperidol) (~25%)	Critically ill patients	[44, 45]		
	80 mg i.v. (total dosage 915 mg over 7 days) (184 ms)	Case report	[46]		
	> 100 mg i.v. over 24 hours (~200 ms)	Critically ill patients	[47]		
Droperidol	0.1 mg·kg i.v. (37 ms)	Surgical patients	[49]		
Pimozide	6 mg orally (13.3 ms)	Healthy volunteers	[50]		
Sertindole	8–20 mg daily (~19 ms)	Patients in clinical trial	[51]	Inhibition of HERG K^+ channels (IC_{50} = 14 nmol·l^{-1})	[52]
Anti-depressants					
Desipramine	2.5 mg·kg^{-1} daily (40 ms)	Case report	[53]	Micromolar concentrations of imipramine (which is metabolised to desipramine) inhibit I_{Kr}	[54, 55]
Nortriptyline	0.51 mg·kg^{-1} daily (46 ms)	Case report	[56]		
Amitriptyline	No significant ΔQTc with 150–200 mg daily	Patients in clinical trial	[57]	Inhibition of heterologously expressed HERG potassium channels (micromolar concentrations)	[54]
Doxepin	Mean dose: 169 mg daily (22 ms)	Patients in clinical trial	[58]		
Fluoxetine	No significant ΔQTc up to a mean dose of 37 mg daily	Patients in clinical trial	[58]	Fluoxetine and its main metabolite norfluoxetine are CYP2D6 and 3A4 isoenzyme inhibitors	[51]
	No significant ΔQTc with 60–80 mg daily	Patients in clinical trial	[57]		
Anti-histamines					
Terfenadine	See Table 3			I_{Kr} inhibition via blockade of HERG K^+ channels	[59, 60, 61, 62]
				Kv1.5 inhibition (10-fold lower activity); at higher concentrations: I_{Na}, I_{Ca}, I_{Ks}, I_{K1}, I_{to} and $I_{K,ATP}$ inhibition	[59, 63, 64, 65, 66, 67, 68, 69]
				No significant difference in antihistamine activity and K_v1.5 inhibition between terfenadine enantiomers	[70, 71]
Astemizole	See Table 3			I_{Kr} inhibition (both astemizole and desmethylastemizole); I_{K1}, I_{to} inhibition	[24, 68, 72]
Mizolastine	No significant ΔQTc up to 40 mg daily	Healthy volunteers	[73]		

Fexofenadine	No significant ΔQTc up to 240 mg daily for 12 months	Healthy volunteers and patients with allergic rhinitis	[74]	Metabolite of terfenadine, considered free of arrhythmic potential	[59]
	180 mg daily (from 10 to 38 ms depending on the formula used to correct QT value)	Case report in susceptible patient	[75, 76]		
Loratadine	No significant ΔQTc up to 10 mg daily combined with 500 mg erythromycin	Healthy volunteers	[77]	Virtually inactive on HERG K^+ channels in non-human models and/or at room temperature	[78, 79]
				Inhibition of HERG K^+ channels in HEK 293 cells (IC_{50} = 173 $nmol \cdot l^{-1}$) at a pacing rate of 0.1 Hz and 37 °C	[62]
				Kv1.5 inhibition; I_{to} inhibition in human atrium especially at 1–2 Hz pacing rate (relevance for rare cases of supraventricular arrhythmias?)	[80]
Cetirizine	No significant ΔQTc up to 60 mg daily	Healthy volunteers	[81]	No effect on HERG K^+ channel up to 30 μM	[79]
				I_{Kr} inhibition only at high concentration	[82]
Macrolides					
Erythromycin	500 mg i.v. infusion (20 ms)	Patients with pneumonia	[83]	CYP3A4 isoenzyme inhibitor	
	Mean dose: 42 $mg \cdot kg^{-1}$ daily i.v. (51 ms)	Retrospective study on all inpatients	[84]	I_{Kr} inhibition and, at higher doses, I_{Na} inhibition	[88]
	500–1,000 mg q.i.d. i.v. (220–278 ms)	Case reports	[85, 86]	Kv1.5 inhibition	[89]
	500–1,000 mg i.v. over 55–90 min (31 ms)	Critically ill patients	[87]		
Spiramycin	350,000 IU kg^{-1} daily (36 ms) orally	Newborns	[90]	No effect on CYP3A4 isoenzyme	[92]
	700,000 IU b.i.d. (135 ms) orally	Newborn	[91]		
Clarithromycin	500 mg b.i.d orally (3 ms)	Healthy volunteers	[93]	CYP3A4 isoenzyme inhibitor	
	500 mg b.i.d. orally (240 and 355 ms)	2 Critically ill patients (cor pulmonale, liver failure, renal failure)	[94]		
Anti-malarials				QTc changes may be associated with *falciparum* malaria independently of antimalarial therapy	[95]
Halofantrine	1000 mg daily (ΔQT ~ 80 ms)	Case report	[96]	The increase in QTc is dose-dependent and treatment with mefloquine during the previous month increases the slope of the halofantrine dose-response curve	[97]
Quinine	No significant ΔQTc up to 1800 mg daily (in a twice-daily oral dosing regimen)	Patients with arrhythmia	[98]	The stereoisomer quinidine is a class-IA anti-arrhythmic endowed also with class-III properties	[102, 103]
	600 mg i.v. t.i.d. (80 ms)	Patients with falciparum malaria	[99]		
	8.3 $mg \cdot kg^{-1}$ i.v. t.i.d. (41 ms)	Case in a clinical trial	[100]		
	10 $mg \cdot kg^{-1}$ i.v. infusion (ΔQTc ≤ 25%)	Healthy volunteers and patients with hepatitis	[101]		
Artemisinin and derivatives	Different regimens of artemisinin derivatives (prolonged QT values in 1.2% of 2638 patients)	Retrospective review of published and unpublished trials	[104]		
	No significant ΔQTc after a single oral dose of 100 mg artemether	Healthy volunteers	[105]		

Table 2 (Contd.)

	Dose associated with QTc increase (ΔQTc recorded)[b]	Population	Reference	Possible mechanism(s) of action and additional information	Reference
	i.m. Artemether (4 $mg \cdot kg^{-1}$ followed by 2 $mg \cdot kg^{-1}$ every 8 h for 72 h) vs i.m. quinine (20 $mg \cdot kg^{-1}$ followed by 10 $mg \cdot kg^{-1}$ every 8 h for 72 h): QT > 500 ms in 25% and 45% of patients, respectively	Patients with severe malaria	[106]		
Quinolones					
Gatifloxacin	200–800 mg (~ 3 ms)	[Data from the summary of the product characteristics]			
Grepafloxacin	600 mg daily (~ 2 ms)	Elderly subjects	[107]		
Levofloxacin	500 mg once daily (127 ms)	Case report (elderly woman with atrial fibrillation)	[108]		
Moxifloxacin	400 mg (6 ms)	[Data from the summary of the product characteristics]		Threshold concentration for class-III anti-arrhythmic effect: ~50 $\mu mol \cdot l^{-1}$	[109]
Sparfloxacin	200–400 mg single oral dose (4%)	Healthy volunteers	[110]	Increases in QTc are dose-related	[112]
	300–400 mg daily after loading dose (20–30 ms)	Healthy volunteers	[32]	Class-III anti-arrhythmic effects in vitro at concentrations ≥10 $\mu mol \cdot l^{-1}$	[113]
	200 mg daily for 10 days after loading dose (~10 ms)	Patients in phase-III trial	[111]		
Miscellanea					
Cisapride	10 mg q.i.d. (6 ms cisapride alone vs 25–26 ms if combined with clarithromycin)	Healthy volunteers	[93]	I_{Kr} inhibition via blockade of HERG K^+ channel ($IC_{50} = 6.5$–44.5 $nmol \cdot l^{-1}$)	[119, 120, 121, 122]
	Mean dose: 0.67 $mg \cdot kg^{-1}$ daily (10 ms)	Paediatric patients	[114]		
	Mean dose: 0.78 $mg \cdot kg^{-1}$ daily (31 ms)	Infants < 3 months of age	[115]		
	Mean dose: 0.81 $mg \cdot kg^{-1}$ daily (15.5 ms)	Paediatric patients	[116]		
	Mean dose: 0.84 $mg \cdot kg^{-1}$ daily (23 ms)	Newborns	[117]		
	Mean dose: 1.31 $mg \cdot kg^{-1}$ daily (74 ms)	Paediatric patients	[118]		
Glibenclamide	1.25–5 mg daily (11.4 ms)	Patients with type-2 diabetes mellitus compared with patients on diet only (but with lower prevalence of diabetic complications)	[123]	Autonomic neuropathy may per se prolong the QT interval	
				Inhibition of I_{to1}; blockade of HERG K^+ channels ($IC_{50} = 74$ $\mu mol \cdot l^{-1}$, i.e. above therapeutic concentrations)	[124, 125]
Ketanserin	40 mg daily (~130 ms)	Elderly patient	[126]	Class-III anti-arrhythmic effect (micromolar concentrations)	[129]
	40 mg b.i.d. (> 30 ms)	30% of patients in a clinical trial	[127]		
	40–80 mg daily (58 ms)	Six patients analysed retrospectively	[128]		
Ketoconazole	400 mg daily (5–10% increase in QTc in ~20% of 55 subjects)	Healthy volunteers	[130]	CYP3A4 inhibitor	
	200 mg b.i.d. orally (5.5 ms)	Healthy volunteers	[131]	I_{Kr} inhibition via blockade of HERG K^+ channels ($IC_{50} = 49$ $\mu mol \cdot l^{-1}$)	[132]
				In animal models, high doses of ketoconazole may mask the QT prolonging effect of H_1-receptor antagonists	[133]
Pentamidine	4 $mg \cdot kg^{-1}$ daily (120 ms)	HIV-infected patients	[134]		

Probucol	500 mg daily (13 ms)	Patients with hyperlipoproteinaemia	[135]		
	1000 mg daily (22 ms)	Patients with hypercholesterolaemia	[136]		
	Mean: 631 mg daily (45 ms)	Patients with hypercholesterolaemia	[137]		
	500 mg b.i.d. (160 ms)	Case report	[138]		
	500–1000 mg daily (QTc values ≥470 ms in 8% of women and 2% of men)	Retrospective review of published reports	[139]		
Tacrolimus (FK506)	2.5 mg i.v. b.i.d. (138 ms)	Case report (baseline QTc > 450 ms)	[140]	I_{to} and I_K inhibition	[144]
	Dose not reported (52 ms)	Case report (concurrent treatment with digoxin)	[141, 142]		
	$0.25\ mg \cdot h^{-1}$ i.v. (300 ms)	Case report	[143]		
Tamoxifen	$100\ mg \cdot m^{-2}$ b.i.d. per os	2 Children in phase 1 study of high dose tamoxifen for refractory malignant gliomas	[145]	I_{Kr} and I_{Ca} inhibition (micromolar concentrations); concentrations causing sub-maximal inhibition of I_{Kr} have no significant effect on action potential duration	[147]
	$\geq 80\ mg \cdot m^{-2}$ b.i.d. per os (10–20%)	Chemotherapy phase-I study in adult patients (combined with vinblastine)	[146]		
Terodiline	12.5 – 25 mg b.i.d. (20–300 ms)	Case series	[148]	I_{Kr} inhibition, I_{Ks} inhibition (20-fold lower activity than on I_{Kr}); I_{K1} inhibition	[151, 152, 153]
	12.5 mg b.i.d. (15 ms)	Elderly patients	[149]	$I_{Ca\text{-}L}$ inhibition and V_{max} reduction	[154]
	200 mg single dose (23 ms)	Healthy volunteers	[150]	R(+) enantiomer seems to be responsible for increased QTc	[150]

[a] The table includes some compounds that have been tested for their QT-prolonging potential, although they were found to have no effect on the QT interval at therapeutically effective doses

[b] ΔQTc (expressed in ms or as percentage variation) is provided where available: results from different studies may not be comparable because of different formulas used to correct the QT value

Table 3 Synopsis of pharmacodynamic and pharmacokinetic parameters in relation to the QT-prolonging potential of terfenadine and astemizole

	Terfenadine			Astemizole		
Dose associated with QTc increase (ΔQTc recorded)	60 mg b.i.d. (6–12 ms) 180 mg b.i.d. (19–26 ms)	Human subjects (healthy volunteers and patients with cardiovascular disease)	[155]	10 mg daily (86 ms)	Case report	[162]
				10 mg t.i.d. combined with erythromycin 250 mg q.i.d. (230 ms)	Case report	[163]
	60 mg b.i.d. combined with erythromycin 500 mg t.i.d. (64 ms)	Healthy volunteers (poor metabolisers)	[156]	10–20 mg daily combined with ketoconazole 50 mg daily (150 ms)	Case report	[164]
	60 mg b.i.d. combined with ketoconazole 200 mg b.i.d. (226 ms)	Case report	[157]			
	120 mg daily combined with ketoconazole 200 mg (100 ms)	Case report	[158]			
	60 mg b.i.d. combined with ketoconazole 200 mg b.i.d. (82 ms)	Healthy volunteers	[159]			
	120 mg daily combined with itraconazole 200 mg daily (41 ms)	Healthy volunteers	[160]			
	60 mg b.i.d. combined with grapefruit juice (19 ms)	Healthy volunteers (poor metabolisers)	[161]			
Concentration causing prolongation of action potential duration	10–30 $nmol \cdot l^{-1}$	Guinea pig ventricular myocytes	[60]	0.3–1.0 $nmol \cdot l^{-1}$	Guinea pig ventricular myocytes	[60]
				> 100 $nmol \cdot l^{-1}$	Rabbit purkinje fibres	[165]
Inhibition of I_{Kr} (IC_{50})	50 $nmol \cdot l^{-1}$	Guinea pig ventricular myocytes	[60]	1.5 $nmol \cdot l^{-1}$	Guinea pig ventricular myocytes	[60]
	96 $nmol \cdot l^{-1}$	Rabbit ventricular myocytes	[82]			
	180 $nmol \cdot l^{-1}$	Cat ventricular myocytes	[166]			
Inhibition of HERG K^{+} channels (IC_{50})	56.0 $nmol \cdot l^{-1}$	Expressed in mouse L cells	[119]	48 $nmol \cdot l^{-1}$	Expressed in *Xenopus laevis* frog oocytes	[61]
	250–350 $nmol \cdot l^{-1}$	Expressed in *Xenopus laevis* frog oocytes	[61, 79, 167]	0.9 $nmol \cdot l^{-1}$	Expressed in HEK 293 cells	[24]
	204 $nmol \cdot l^{-1}$	Expressed in HEK 293 cells	[62]			
Inhibition of I_{Ks} (IC_{50})	~10,000 $nmol \cdot l^{-1}$	Guinea pig ventricular myocytes	[168]	No effect		[60]
Plasma concentration achieved at therapeutic doses (60–120 mg daily for terfenadine and 10 mg daily for astemizole)	Parent terfenadine usually undetectable (< 11 $nmol \cdot l^{-1}$)		[169]	Steady-state concentration: 0.28 $nmol \cdot l^{-1}$ (astemizole) ~11 $nmol \cdot l^{-1}$ (astemizole + desmethylastemizole)		[170]
	Peak concentration in poor metabolisers: 17 $nmol \cdot l^{-1}$		[161]			

Peak plasma concentrations reported during concomitant administration of CYP3A4 inhibitors (concentrations refer to the parent compound unless otherwise specified)	42 nmol·l^{-1}	With erythromycin in healthy volunteers (3 of 9 subjects)	[156]	1.8 nmol·l^{-1}	With itraconazole in healthy volunteers	[176]
	16 nmol·l^{-1}	With erythromycin in healthy volunteers (3 of 6 subjects)	[171]	0.9 nmol·l^{-1} (desmethylastemizole)	With itraconazole in healthy volunteers	[176]
	19 nmol·l^{-1}	With clarithromycin in healthy volunteers (4 of 6 subjects)	[171]			
	121 nmol·l^{-1}	With ketoconazole in case report	[157]			
	~53–170 nmol·l^{-1}	With ketoconazole in healthy volunteers (5 of 6 subjects)	[159]			
	59–204 nmol·l^{-1} (peak?)	With itraconazole in 2 case reports	[172, 173]			
	21–42 nmol·l^{-1}	With itraconazole in healthy volunteers	[160]			
	15–25 nmol·l^{-1}	With grapefruit juice in healthy volunteers	[161, 174, 175]			
% Plasma protein binding	97		[177]	97		[178]
Volume of distribution	Not reported		[178]	~45 l·kg^{-1}		[170]
Main metabolites	Fexofenadine (MDL 16455; terfenadine carboxylate): H_1-receptor antagonist with no effect on QT interval			Desmethylastemizole (same activity as parent compound as H_1-receptor antagonist and HERG K$^+$ channel blocker with an apparent elimination half-life of 9.5 days), norastemizole, 6-hydroxy-desmethylastemizole		[24, 170]
Relative risk (adjusted for age and gender) for ventricular arrhythmias (non use = 1; case control analysis)	2.0		[27]	17.8		[27]

6

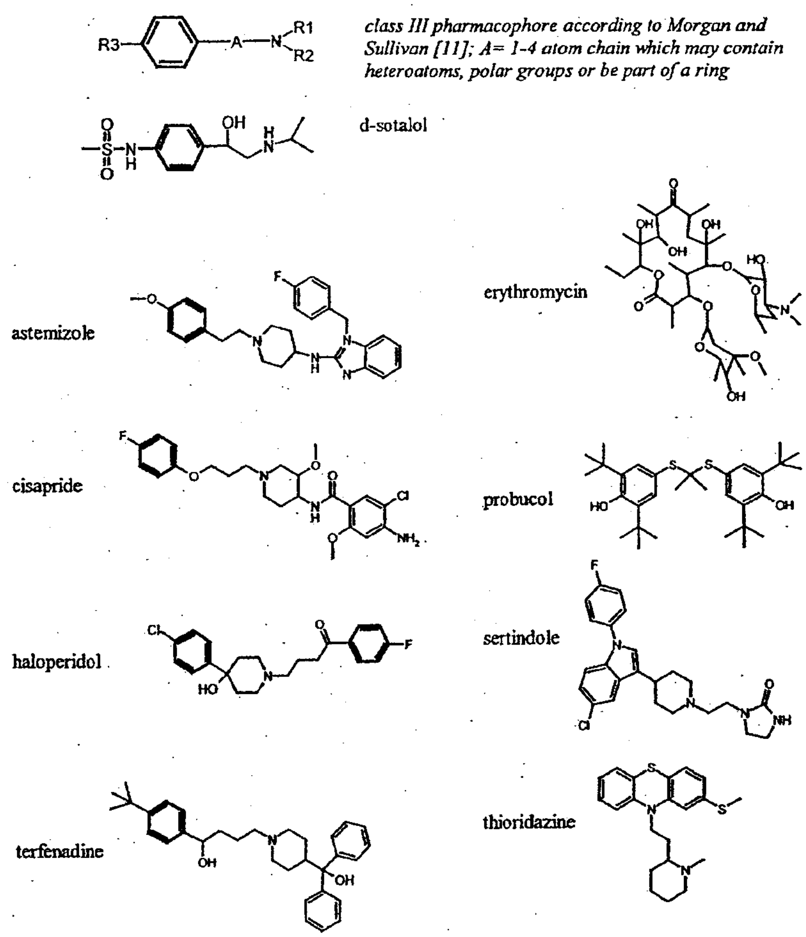


Fig. 2 Molecular structures of some drugs associated with QT-prolongation or torsades de pointes in relation to the pharmacophore proposed to carry class-III antiarrhythmic properties by Morgan and Sullivan [11]. On the *left*, examples of drugs in which this pharmacophore (a phenyl ring connected to a basic nitrogen via a linking chain) can be recognised. On the *right*, examples of drugs with reported QT-prolonging potential in which this pharmacophore is not easily identifiable

effects or that currents other than HERG-related K^+ currents are responsible for QT-interval prolongation and/or occurrence of life-threatening arrhythmias. In addition, lipophilicity and/or bulkiness of substitutions on the molecular structure may be crucial parameters conferring varying degrees of K^+-channel-blocking activity. For instance, terfenadine carboxylate (fexofenadine), the main metabolite of terfenadine, is a more polar compound having virtually no effects on QTc, apart from an isolated report in a susceptible patient (Table 2).

In any case, an important acquisition of the past decade is that cardiac adverse effects are not necessarily an intrinsic class effect: in the case of H_1-receptor antagonists [1], there is no correlation between the antihistaminic potency and the action potential prolonging effect. Likewise, as regards gastrointestinal prokinetic agents (in particular, $5\text{-}HT_4$ receptor agonists), several lines of evidence suggest that blockade of HERG K^+ channels rather than stimulation of atrial $5\text{-}HT_4$ receptors is responsible for QT prolongation [12, 13].

Interpretation of data from preclinical/in vitro studies

The role of preclinical screening methods is highly debated, because of the inherent differences between animal models and humans. However, a recent review [14] shows that, if properly conducted, in vitro and in vivo assessment of class-III properties of an investigational drug provides useful information and suggests that either method alone may be sufficient for the preclinical evaluation of the QT-prolonging potential. Several laboratories are indeed refining methods to study this aspect in animal models [15, 16, 17, 18, 19, 20, 21]. Although in vitro electrophysiological studies offer valuable information on arrhythmogenic mechanism(s), it should be kept in mind that proving that a drug has no effect on HERG-related currents does not automatically rule out the possibility of a clinically significant prolongation of the QT interval or the risk of potentially harmful arrhythmias. By contrast, detection of an effect on potassium channels does not invariably raise serious QT-related concerns on the clinical use of the

compound. For instance, the 5-HT_3-receptor antagonist ondansetron prolongs action potential duration by blocking I_K with a K_D of 1.7 μM in feline ventricular myocytes [22] and prolongs the QTc interval in dogs at doses of 2.63 $mg \cdot kg^{-1}$ i.v. or more [23]. However, present clinical experience and the fact that concentrations blocking I_K are well above concentrations at which 5-HT_3 receptors are inhibited do not suggest a significant cardiotoxic potential.

A major problem in interpreting results obtained in preclinical/in vitro electrophysiological studies (IC_{50} for inhibition of K^+ currents, IC_{50} for prolongation of action potential duration, etc.) is that a careful scrutiny of the pharmacokinetic properties of the compound is mandatory to allow meaningful comparisons between in vitro and plasma concentrations. Plasma concentrations in humans should be considered along with the apparent volume of distribution, the metabolic pathways (metabolites may retain QT prolonging potential, be even more active, or be devoid of such an effect), and the mode of elimination. The threshold concentration (or the IC_{50}) for a class-III effect in vitro may be higher than peak plasma concentrations achieved at therapeutic doses, but tissue concentrations (specifically, cardiac tissue concentrations) may exceed those found in plasma if the drug has a large volume of distribution. One example is provided by the comparison of pharmacodynamic/pharmacokinetic parameters of terfenadine and astemizole reported in Table 3. Terfenadine is readily metabolised to fexofenadine, which maintains good H_1-receptor blocking activity, but has no effect on the QT interval even at doses well above the therapeutic ones. Unmetabolised terfenadine plasma concentrations are usually below detection limits (5 $ng \cdot ml^{-1}$ or 11 $nmol \cdot l^{-1}$, in most studies), but may become detectable in case of pharmacokinetic interactions with drugs known to inhibit the CYP3A4 isoenzyme, in case of overdosage or concomitant hepatic disease. On the contrary, two of the main metabolites of astemizole (desmethylastemizole and norastemizole) retain the ability to block HERG K^+ currents at nanomolar concentrations [24]. In addition, the large volume of distribution of astemizole (indicating extensive tissue penetration: indeed, the concentration in cardiac muscle is estimated to be more than 100 times as high as the plasma concentration [25, 26]) and the long elimination half-life of desmethylastemizole (about 9.5 days) suggest a higher risk of potentially harmful effects on cardiac repolarisation with astemizole than with terfenadine. This prediction based on pharmacokinetic/pharmacodynamic data is in good agreement with a recent case-control study, which calculated that the relative risk of ventricular arrhythmias (adjusted for age and gender) was 2.0 for terfenadine and 17.8 for astemizole (non-use = 1) [27].

Clinical relevance

Although asymptomatic prolongation of the QT interval is a useful marker of the cardiotoxic potential of a drug, it is only a surrogate marker of cardiotoxicity and it is difficult to establish the threshold for a clinically significant prolongation of the QT interval. Thus, identification of risk factors that may precipitate prolongation of the QT interval into life-threatening arrhythmias becomes an important issue (see Table 4 for a synopsis). Widespread knowledge of these risk factors should help to avoid misprescriptions leading to cardiotoxicity.

The clinical use of drugs that are known to prolong the QT interval is not necessarily associated with an increased occurrence of ventricular arrhythmias, unless high dosage, i.v. route of administration (especially at high injection rates: e.g. erythromycin) or concomitant metabolic inhibitors are used or other risk factors (Table 4) coexist. For instance, a recent study suggests that long-term anti-psychotic medication at conventional doses does not increase ventricular tachyarrhythmias in patients without cardiac disease, despite evidence for prolonged QTc interval and QTc dispersion [2]. Further clinical studies with appropriate statistical power should evaluate the cardiotoxic potential of currently licensed drugs that fall into one of those classes

Table 4 Risk factors for the occurrence of torsades de pointes[a]

Subject related
Congenital long QT syndrome; QTc > 440 ms; increased QT dispersion
Female gender
Clinically significant bradycardia (< 50 beats per minute), history of symptomatic arrhythmias or any other clinically significant heart disease
Electrolyte imbalance (especially hypokalaemia, hypomagnesaemia)
Impaired hepatic/renal function
Hypothyroidism
Drug-related
Concomitant treatment with drugs with known potential for
Pharmacokinetic interactions with CYP3A4 isoenzyme inhibitors: e.g., serotonin reuptake inhibitors, HIV protease inhibitors, zileuton
Pharmacokinetic (inhibition of CYP3A isoenzyme)/pharmacodynamic (intrinsic class III effect) interactions: e.g. macrolide antibacterials (e.g. erythromycin), azole antifungals (e.g. ketoconazole)
Pharmacodynamic interactions: e.g. anti-arrhythmics (class I and III), drugs inducing electrolyte imbalance such as diuretics (risk of hypokalaemia)

[a] A recent paper provides useful information to discriminate electrocardiographic artefacts mimicking ventricular tachycardia [179].

with recognised QT-prolonging effect and guide the risk–benefit assessment of these compounds.

Concerning newly licensed drugs, the availability of many new agents and changes in medication consumption patterns over the years threaten to exacerbate problems such as misprescribing, medication errors and undetected interactions. In this setting, post-marketing surveillance becomes essential in ensuring drug safety [28]. Although the right solution to misprescribing of a useful drug with a significant, albeit minor, cardiotoxic potential is not necessarily its withdrawal from the market, it should be acknowledged that, in some cases, the complexities of prescribing information may be difficult to implement. The potential for drug interactions (namely those inhibiting the CYP3A4 isoenzyme [29]) is receiving increasing attention both from drug companies and regulatory agencies. The withdrawal of mibefradil in 1998 may be taken as an example of a drug with a sound pharmacological rationale that was difficult to use in a clinical setting because of the potential for drug interactions via CYP3A4 isoenzyme inhibition.

Standardization of procedures for regulatory purposes

There are several recent examples of the great impact that the finding of a QT-prolonging effect by non-cardiac drugs during clinical trials has on drug development [30, 31]. A recent paper [32] outlines the various actions that were taken in phase I–III studies to evaluate the electrocardiographic and cardiovascular safety data of sparfloxacin in accordance with the suggestions of an independent international safety board.

The ongoing discussion on the QT-prolonging potential of non-cardiac drugs and its clinical significance does not allow us to provide strict guidelines to standardise procedures to be followed in the event that a new investigational drug turns out to affect the QT interval. However, the European Agency (EMEA) issued a document [33] that offers a useful starting point and should be revised periodically to keep pace with ongoing developments. In this document, the problems encountered in obtaining reliable and meaningful measurements of drug-induced changes of the QT interval in preclinical and clinical studies are briefly discussed. These problems are also outlined in Table 5.

Several authors have already drawn the attention to the inherent difficulties involved in accurate measurement of the QT interval. A recent review [34] discusses possible answers to issues related to QTc prolongation by non-cardiac drugs (e.g. what is the desired outcome? what is the dependent variable to be measured? what is the appropriate statistical analysis?). For the evaluation of potential clinical risks associated with QTc changes, individual QTc changes rather than mean values for study populations should be used. Moreover, while changes in QTc indicate a drug effect, absolute QTc values have greater prognostic significance for the occurrence of tachyarrhythmias. In the EMEA document [33], the following general guidelines are given on QTc changes (using the Bazett's correction) relative to baseline measurements (see also [34] for a discussion): (1) individual changes below 30 ms are generally thought unlikely to raise significant concerns about the potential risk of arrhythmias; (2) individual changes between 30 ms and 60 ms are more likely to represent a drug effect and raise concern about the potential risk of arrhythmias; and (3) individual changes greater than 60 ms raise clear concerns about the potential risk of arrhythmias.

The possible use of QT dispersion rather than QT prolongation as a risk predictor is also being investi-

Table 5 Problems encountered in obtaining reliable and meaningful measurements of drug-induced changes of the QT interval

Patient variability
High intraindividual (circadian variation; law of regression to the mean [180]) and interindividual variability (males vs females; infants vs adults) in QTc values
Variability in the individual metabolic capacity for a given drug
Measurement of QT interval
Variability in the heart rate (different formulas to correct the QT value for heart rate)
Changes in T wave morphology and occurrence of U waves (may be important warning signs and precede the occurrence of torsades de pointes)
Lack of a strict definition of normal and abnormal values
Lack of reliable correlation between readings from Holter recordings and standard ECG
Lack of standardisation of automated ECG readings
Pharmacokinetics
Timing of ECG measurements with respect to peak/steady state drug plasma concentrations
Need to consider plasma concentrations of both parent drug and its significant metabolites (especially if they display class-III anti-arrhythmic effects)
Need for enantioselective methods to monitor plasma concentrations of racemic compounds
Data analysis and interpretation
Definition of the dependent variable (raw QTc interval vs maximal QTc interval vs maximal QTc change from baseline vs area under the QTc interval-time curve vs QTc dispersion; see ref. [34])
Statistical power of the study
What is the threshold for a clinically significant change in QTc/QT dispersion?

gated [2, 33]. Increased QT dispersion (i.e. the difference between the maximum and minimum QT across the 12-lead ECG) is considered a marker of uneven cardiac repolarisation. Although the cellular basis for QT dispersion is not completely understood, interest in this parameter has been fuelled by the finding in animal studies that increased dispersion lowers the ventricular fibrillation threshold and facilitates induction of re-entrant arrhythmias. Clinically, QT dispersion is being investigated as a predictor of long-term mortality in patients with acute myocardial infarction and clinical evidence of heart failure [35].

Several cases should be considered when characterising the effects of non-cardiac drugs on QTc intervals: a compound may have no effect on QTc; it may have a minor effect that is considered clinically insignificant; and, in rare instances, there may be a clinically significant effect, but the risk at therapeutic doses may be overwhelmed by the benefit achieved in a specific clinical condition for which no alternatives are available.

A crucial issue in the evaluation of studies reporting no effect of a given compound on the QT interval is the statistical power of the study. Insufficient statistical evidence for a difference does not necessarily mean that there is no difference, and studies reporting the effects on QT interval should always discuss their statistical power. This issue should be kept in mind when considering some of the early studies reported in Table 2, which were not specifically designed to detect changes in QT interval.

When a non-cardiac drug significantly affects the QTc interval, the overall clinical significance depends on a number of parameters (dose–response relationship; likelihood of pharmacokinetic interactions, etc.) that should be evaluated in relation to the proposed clinical use. Consistency in this evaluation process for regulatory purposes is mandatory.

Looking for European Public Assessment Reports at the EMEA internet site, we found that documents concerning the following non-cardiac drugs mentioned effects on the QT interval: alatrofloxacin, emedastine, levoacetylmethadol, mizolastine, olanzapine, samarium [^{153}Sm] lexidronam pentasodium, sparfloxacin and trovafloxacin.

Levoacetylmethadol is an example of a drug which, although prolonging the QT interval, was recently licensed by the European Agency (EMEA), with the recommendation to perform additional comparative studies with methadone as well as in vitro electrophysiological studies to evaluate the risk of cardiac conduction and repolarisation changes.

In our opinion, licensing a new non-cardiac drug with QT-prolonging potential, with the recommendation to perform additional studies, may be justified when major innovation is achieved with respect to existing therapies. On the contrary, if the compound does not represent significant innovation, the recommendation to perform additional studies on the QT-prolonging effect should be a prerequisite to obtain marketing authorisation.

Future perspectives

In the next few years, basic and clinical pharmacologists will have to address a number of issues concerning the re-assessment of licensed medicinal products and new drug development.

For currently licensed non-cardiac drugs with QT-prolonging potential, a formal assessment (pharmacoepidemiological studies) of relative risks for patients exposed to these agents will enable a formal risk–benefit assessment and identification of possible additional risk factors due to the underlying disease or concomitant medication. In case risk factors are identified, amendment of the summary of product characteristics is a necessary step, but often turns out to be ineffective to ensure safe drug utilisation. Amendments to the summary of product characteristics combined with "Dear Doctor letters" seems to be a more appropriate action.

For investigational new drugs, the following needs emerge:

1. Structure–activity studies joining the efforts of medicinal chemists and molecular pharmacologists could lead to associate a definite pharmacophore with an action on a specific ion channel, hence on a given portion of the atrial and/or ventricular action potential; this *in silico* approach will help the preclinical development of investigational new drugs.
2. Standardisation of procedures in preclinical in vitro and in vivo studies (especially as regards QT measurements) to screen those molecules having a QT-prolonging potential on the basis of *in silico* predictions.
3. Carefully designed phase I–III studies, especially for those drugs that appear to have a discrete, albeit small, effect on the QT in preclinical tests. In these cases, it would be unwise to try "to prove the null hypothesis" (which, strictly speaking, can never be proven) resorting to studies that claim no difference between drug and placebo with inadequate statistical power. Identifying the percentage of "outliers" (i.e. those patients that have greater QT prolongation) may also be a useful guide to assess risk in subjects treated with a new agent versus comparators. Parallel in vitro electrophysiological studies will help to define the pharmacological profile and cardiotoxic potential of these investigational new drugs and may become part of standard regulatory requirements.

References

1. Zhang MQ (1997) Chemistry underlying the cardiotoxicity of antihistamines. Curr Med Chem 4: 171–184
2. Kitayama H, Kiuchi K, Nejima J, Katoh T, Takano T, Hayakawa H (1999) Long-term treatment with antipsychotic drugs in conventional doses prolonged QTc dispersion, but did not increase ventricular tachyarrhythmias in patients with schizophrenia in the absence of cardiac disease. Eur J Clin Pharmacol 55: 259–262

3. Lipicky RJ (1993) A viewpoint on drugs that prolong the QTc interval. Am J Cardiol 72: 53B–54B
4. Thomas M, Maconochie JG, Fletcher E (1996) The dilemma of the prolonged QT interval in early drug studies. Br J Clin Pharmacol 41: 77–81
5. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J (1991) QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. Circulation 83: 1888–1894
6. Elming H, Holm E, Jun L, Torp-Pedersen C, Kober L, Kirscshoff M, Malik M, Camm J (1998) The prognostic value of the QT interval and QT interval dispersion in all-cause and cardiac mortality and morbidity in a population of Danish citizens. Eur Heart J 19: 1391–1400
7. de Bruyne MC, Hoes AW, Kors JA, Hofman A, van Bemmel JH, Grobbee DE (1999) Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam Study. Eur Heart J 20: 278–284
8. Roden DM, George ALJ (1997) Structure and function of cardiac sodium and potassium channels. Am J Physiol 273: H511–H525
9. Fedida D, Chen FS, Zhang X (1998) The 1997 Stevenson Award Lecture. Cardiac K+ channel gating: cloned delayed rectifier mechanisms and drug modulation. Can J Physiol Pharmacol 76: 77–89
10. Nattel S (1999) The molecular and ionic specificity of antiarrhythmic drug actions. J Cardiovasc Electrophysiol 10: 272–282
11. Morgan TKJ, Sullivan ME (1992) An overview of class III electrophysiological agents: a new generation of antiarrhythmic therapy. Prog Med Chem 29: 65–108
12. Tonini M, De Ponti F, Di Nucci A, Crema F (1999) Review article: cardiac adverse effects of gastrointestinal prokinetics. Alim Pharmacol Ther 13: 1585–1591
13. Crema F, Modini C, Croci T, Langlois M, De Ponti F (1999) Intestinal prokinesia by two esters of 4-amino-5-chloro-2-methoxybenzoic acid: involvement of 5-hydroxytryptamine-4 receptors and dissociation from cardiac effects in vivo. J Pharmacol Exp Ther 288: 1045–1052
14. Davis AS (1998) The pre-clinical assessment of QT interval prolongation: a comparison of in vitro and in vivo methods. Hum Exp Toxicol 17: 677–680
15. Drici MD, Ebert SN, Wang WX, Rodriguez I, Liu XK, Whitfield BH, Woosley RL (1999) Comparison of tegaserod (HTF 919) and its main human metabolite with cisapride and erythromycin on cardiac repolarization in the isolated rabbit heart. J Cardiovasc Pharmacol 34: 82–88
16. Matsunaga T, Mitsui T, Harada T, Inokuma M, Murano H, Shibutani Y (1998) QT corrected for heart rate and relation between QT and RR intervals in beagle dogs. J Pharmacol Toxicol Methods 38: 201–209
17. Matsunaga T, Harada T, Inokuma M, Mitsui T, Duffy PA, Aldridge A, Shibutani Y (1999) QT prolongation and torsades de pointes induced by an antifungal agent, D0870, in conscious dogs. Toxicology 132: 187–199
18. Usui T, Sugiyama A, Ishida Y, Satoh Y, Sasaki Y, Hashimoto K (1998) Simultaneous assessment of the hemodynamic, cardiomechanical, and electrophysiological effects of terfenadine on the in vivo canine model. Heart Vessels 13: 49–57
19. D'Alonzo AJ, Zhu JL, Darbenzio RB (1999) Effects of class III antiarrhythmic agents in an in vitro rabbit model of spontaneous torsades de pointe. Eur J Pharmacol 369: 57–64
20. Ohmura T, Chachin M, Tarui S, Nagakura A, Igarashi T, Ikeda H, Ikegami K, Kitagawa H, Uchida S (1999) Effects of terfenadine, astemizole and epinastine on electrocardiogram in conscious cynomolgus monkeys. Eur J Pharmacol 378: 169–175
21. Weissenburger J, Noyer M, Cheymol G, Jaillon P (1999) Electrophysiological effects of cetirizine, astemizole and D-sotalol in a canine model of long QT syndrome. Clin Exp Allergy 29[suppl 3]: 190–196
22. de Lorenzi FG, Bridal TR, Spinelli W (1994) Block of the delayed rectifier current (IK) by the 5-HT3 antagonists ondansetron and granisetron in feline ventricular myocytes. Br J Pharmacol 113: 527–535
23. Williams PD, Cohen ML, Turk JA (1991) Electrocardiographic effects of zatosetron and ondansetron, two $5HT_3$ receptor antagonists, in anesthetized dogs. Drug Dev Res 24: 277–284
24. Zhou Z, Vorperian VR, Gong Q, Zhang S, January CT (1999) Block of HERG potassium channels by the antihistamine astemizole and its metabolites desmethylastemizole and norastemizole. J Cardiovasc Electrophysiol 10: 836–843
25. Michiels M, Van Peer A, Woestenborghs R, Heykants J (1986) Pharmacokinetics and tissue distribution of astemizole in the dog. Drug Dev Res 8: 53–62
26. Sugiyama A, Aye NN, Katahira S, Saitoh M, Hagihara A, Matsubara Y, Hashimoto K (1997) Effects of nonsedating antihistamine, astemizole, on the in situ canine heart assessed by cardiohemodynamic and monophasic action potential monitoring. Toxicol Appl Pharmacol 143: 89–95
27. de Abajo FJ, Rodriguez LA (1999) Risk of ventricular arrhythmias associated with nonsedating antihistamine drugs. Br J Clin Pharmacol 47: 307–313
28. McMullin ST, Reichley RM, Watson LA, Steib SA, Frisse ME, Bailey TC (1999) Impact of a web-based clinical information system on cisapride drug interactions and patient safety. Arch Intern Med 159: 2077–2082
29. Ekins S, Bravi G, Binkley S, Gillespie JS, Ring BJ, Wikel JH, Wrighton SA (1999) Three- and four-dimensional quantitative structure activity relationship analyses of cytochrome P-450 3A4 inhibitors. J Pharmacol Exp Ther 290: 429–438
30. Stupp R, Bauer J, Pagani O, Gerard B, Cerny T, Sessa C, Bastian G, Sarkany M, Schlapfer J, Giroux B, Leyvraz S (1998) Ventricular arrhythmia and torsade de pointe: dose limiting toxicities of the MDR-modulator S9788 in a phase I trial. Ann Oncol 9: 1233–1242
31. Stevenson JP, DeMaria D, Reilly D, Purvis JD, Graham MA, Lockwood G, Drozd M, O'Dwyer PJ (1999) Phase I/pharmacokinetic trial of the novel thioxanthone SR233377 (WIN33377) on a 5-day schedule. Cancer Chemother Pharmacol 44: 228–234
32. Jaillon P, Morganroth J, Brumpt I, Talbot G (1996) Overview of electrocardiographic and cardiovascular safety data for sparfloxacin. Sparfloxacin Safety Group. J Antimicrob Chemother 37[suppl A]: 161–167
33. Anonymous (1997) Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. European Agency for the Evaluation of Medicinal Products (EMEA): Committee for Proprietary Medicinal Products (CMPMP)
34. Bonate PL, Russell T (1999) Assessment of QTc prolongation for non-cardiac-related drugs from a drug development perspective. J Clin Pharmacol 39: 349–358
35. Spargias KS, Lindsay SJ, Kawar GI, Greenwood DC, Cowan JC, Ball SG, Hall AS (1999) QT dispersion as a predictor of long-term mortality in patients with acute myocardial infarction and clinical evidence of heart failure. Eur Heart J 20: 1158–1165
36. Warner JP, Barnes TR, Henry JA (1996) Electrocardiographic changes in patients receiving neuroleptic medication. Acta Psychiatr Scand 93: 311–313
37. Adamantidis MM, Kerram P, Dupuis BA (1994) In vitro electrophysiological detection of iatrogenic arrhythmogenicity. Fundam Clin Pharmacol 8: 391–407
38. Drici MD, Wang WX, Liu XK, Woosley RL, Flockhart DA (1998) Prolongation of QT interval in isolated feline hearts by antipsychotic drugs. J Clin Psychopharmacol 18: 477–481
39. Hartigan-Go K, Bateman DN, Nyberg G, Martensson E, Thomas SH (1996) Concentration-related pharmacodynamic effects of thioridazine and its metabolites in humans. Clin Pharmacol Ther 60: 543–553

40. Bastecky J, Kvasnicka J, Vortel J, Zapletalek M, Hanus M, Kasparova V, Wasylisova V (1990) Suicidal ingestion of thioridazine as a cause of severe impairment of heart rhythm-polymorphic ventricular tachycardia (in Czech). Cesk Psychiatry 86: 264–268
41. Ochiai H, Kashiwagi M, Usui T, Oyama Y, Tokita Y, Ishikawa T (1990) Torsade de Pointes with T wave alternans in a patient receiving moderate dose of chlorpromazine: report of a case (in Japanese). Kokyu To Junkan 38: 819–822
42. Jackson T, Ditmanson L, Phibbs B (1997) Torsade de pointes and low-dose oral haloperidol. Arch Intern Med 157: 2013–2015
43. Kriwisky M, Perry GY, Tarchitsky D, Gutman Y, Kishon Y (1998) Haloperidol-induced torsades de pointes. Chest 98: 482–484
44. Lawrence KR, Nasraway SA (1997) Conduction disturbances associated with administration of butyrophenone antipsychotics in the critically ill: a review of the literature. Pharmacotherapy 17: 531–537
45. Metzger E, Friedman R (1993) Prolongation of the corrected QT and torsades de pointes cardiac arrhythmia associated with intravenous haloperidol in the medically ill. J Clin Psychopharmacol 13: 128–132
46. O'Brien JM, Rockwood RP, Suh KI (1999) Haloperidol-induced torsade de pointes. Ann Pharmacother 33: 1046–1050
47. Wilt JL, Minnema AM, Johnson RF, Rosenblum AM (1993) Torsade de pointes associated with the use of intravenous haloperidol. Ann Intern Med 119: 391–394
48. Suessbrich H, Schonherr R, Heinemann SH, Attali B, Lang F, Busch AE (1997) The inhibitory effect of the antipsychotic drug haloperidol on HERG potassium channels expressed in Xenopus oocytes. Br J Pharmacol 120: 968–974
49. Lischke V, Behne M, Doelken P, Schledt U, Probst S, Vettermann J (1994) Droperidol causes a dose-dependent prolongation of the QT interval. Anesthes Analg 79: 983–986
50. Desta Z, Kerbusch T, Flockhart DA (1999) Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimozide in healthy poor and extensive metabolizers of cytochrome P450 2D6 (CYP2D6). Clin Pharmacol Ther 65: 10–20
51. van Kammen DP, McEvoy JP, Targum SD, Kardatzke D, Sebree TB (1996) A randomized, controlled, dose-ranging trial of sertindole in patients with schizophrenia. Psychopharmacology (Berl) 124: 168–175
52. Rampe D, Murawsky MK, Grau J, Lewis EW (1998) The antipsychotic agent sertindole is a high affinity antagonist of the human cardiac potassium channel HERG. J Pharmacol Exp Ther 286: 788–793
53. Wagner KD, Fershtman M (1993) Potential mechanism of desipramine-related sudden death in children. Psychosomatics 34: 80–83
54. Teschemacher AG, Seward EP, Hancox JC, Witchel HJ (1999) Inhibition of the current of heterologously expressed HERG potassium channels by imipramine and amitriptyline. Br J Pharmacol 128: 479–485
55. Valenzuela C, Sánchez-Chapula J, Delpón E, Elizalde A, Pérez O, Tamargo J (1994) Imipramine blocks rapidly activating and delays slowly activating K^+ current activation in guinea pig ventricular myocytes. Circ Res 74: 687–699
56. Alderton HR (1995) Tricyclic medication in children and the QT interval: case report and discussion. Can J Psychiatry 40: 325–329
57. Upward JW, Edwards JG, Goldie A, Waller DG (1988) Comparative effects of fluoxetine and amitriptyline on cardiac function. Br J Clin Pharmacol 26: 399–402
58. Baker B, Dorian P, Sandor P, Shapiro C, Schell C, Mitchell J, Irvine MJ (1997) Electrocardiographic effects of fluoxetine and doxepin in patients with major depressive disorder. J Clin Psychopharmacol 17: 15–21
59. Roy M, Dumaine R, Brown AM (1996) HERG, a primary human ventricular target of the nonsedating antihistamine terfenadine. Circulation 94: 817–823
60. Salata JJ, Jurkiewicz NK, Wallace AA, Stupienski RF, Guinosso-PJJ, Lynch JJ (1995) Cardiac electrophysiological actions of the histamine H1-receptor antagonists astemizole and terfenadine compared with chlorpheniramine and pyrilamine. Circ Res 76: 110–119
61. Suessbrich H, Waldegger S, Lang F, Busch AE (1996) Blockade of HERG channels expressed in Xenopus oocytes by the histamine receptor antagonists terfenadine and astemizole. FEBS Lett 385: 77–80
62. Crumb WJ (2000) Loratadine blockade of K^+ channels in human heart: comparison with terfenadine under physiological conditions. J Pharmacol Exp Ther 292: 261–264
63. Ming Z, Nordin C (1995) Terfenadine blocks time-dependent $Ca2+$, $Na+$, and $K+$ channels in guinea pig ventricular myocytes. J Cardiovasc Pharmacol 26: 761–769
64. Ducic I, Neville RF, Morad M (1995) Modulation of K^+ currents by antihistamines in rat ventricular myocytes. Biophys J 68: A113
65. Liu S, Melchert RB, Kennedy RH (1997) Inhibition of L-type $Ca2+$ channel current in rat ventricular myocytes by terfenadine. Circ Res 81: 202–210
66. Lu Y, Wang Z (1999) Terfenadine block of sodium current in canine atrial myocytes. J Cardiovasc Pharmacol 33: 507–513
67. Gintant GA (1994) Pharmacologic dissection of delayed rectifier current (I_K) in canine ventricular myocytes by E-4031 and terfenadine: I_{Kr} and I_{Ks} "swap". Biophys J 66: A210
68. Berul CI, Morad M (1995) Regulation of potassium channels by nonsedating antihistamines. Circulation 91: 2220–2225
69. Nishio M, Habuchi Y, Tanaka H, Morikawa J, Yamamoto T, Kashima K (1998) Blockage by terfenadine of the adenosine triphosphate (ATP)-sensitive $K+$ current in rabbit ventricular myocytes. J Pharmacol Exp Ther 287: 293–300
70. Zhang MQ, Timmerman H (1993) Terfenadine: a mixture of equipotent antihistamine enantiomers without a clear 'isomeric ballast'. Pharm World Sci 15: 186–192
71. Yang T, Prakash C, Roden DM, Snyders DJ (1995) Mechanism of block of a human cardiac potassium channel by terfenadine racemate and enantiomers. Br J Pharmacol 115: 267–274
72. Vorperian VR, Zhou Z, Mohammad S, Hoon TJ, Studenik C, January CT (1996) Torsade de pointes with an antihistamine metabolite: potassium channel blockade with desmethylastemizole. J Am Coll Cardiol 28: 1556–1561
73. Chaufour S, Caplain H, Lilienthal N, L'heritier C, Deschamps C, Dubruc C, Rosenzweig P (1999) Study of cardiac repolarization in healthy volunteers performed with mizolastine, a new H1-receptor antagonist. Br J Clin Pharmacol 47: 515–520
74. Pratt CM, Mason J, Russell T, Reynolds R, Ahlbrandt R (1999) Cardiovascular safety of fexofenadine HCl. Am J Cardiol 83: 1451–1454
75. Pinto YM, van Gelder IC, Heeringa M, Crijns HJGM (1999) QT lengthening and life-threatening arrhytmias associated with fexofenadine. Lancet 353: 980
76. Giraud T (1999) QT lengthening and arrhythmias associated with fexofenadine. Lancet 353: 2072–2073
77. Brannan MD, Reidenberg P, Radwanski E, Shneyer L, Lin CC, Cayen MN, Affrime MB (1995) Loratadine administered concomitantly with erythromycin: pharmacokinetic and electrocardiographic evaluations. Clin Pharmacol Ther 58: 269–278
78. Lacerda AE, Roy ML, Lewis EW, Rampe D (1997) Interactions of the nonsedating antihistamine loratadine with a Kv1.5-type potassium channel cloned from human heart. Mol Pharmacol 52: 314–322 (published erratum Mol Pharmacol 52: 754)
79. Taglialatela M, Pannaccione A, Castaldo P, Giorgio G, Zhou Z, January CT, Genovese A, Marone G, Annunziato L (1998) Molecular basis for the lack of HERG K+ channel block-related cardiotoxicity by the H1 receptor blocker cetirizine compared with other second-generation antihistamines. Mol Pharmacol 54: 113–121

80. Crumb WJ (1999) Rate-dependent blockade of a potassium current in human atrium by the antihistamine loratadine. Br J Pharmacol 126: 575–580
81. Sale ME, Barbey JT, Woosley RL, Edwards D, Yeh J, Thakker K, Chung M (1994) The electrocardiographic effects of cetirizine in normal subjects. Clin Pharmacol Ther 56: 295–301
82. Carmeliet E (1998) Effects of cetirizine on the delayed K+ currents in cardiac cells: comparison with terfenadine. Br J Pharmacol 124: 663–668
83. Mishra A, Friedman HS, Sinha AK (1999) The effects of erythromycin on the electrocardiogram. Chest 115: 983–986
84. Oberg KC, Bauman JL (1995) QT interval prolongation and torsades de pointes due to erythromycin lactobionate. Pharmacotherapy 15: 687–692
85. Katapadi K, Kostandy G, Katapadi M, Hussain KM, Schifter D (1997) A review of erythromycin-induced malignant tachyarrhythmia–torsade de pointes. A case report. Angiology 48: 821–826
86. Gitler B, Berger LS, Buffa SD (1994) Torsades de pointes induced by erythromycin. Chest 105: 368–372
87. Tschida SJ, Guay DR, Straka RJ, Hoey LL, Johanning R, Vance BK (1996) QTc-interval prolongation associated with slow intravenous erythromycin lactobionate infusions in critically ill patients: a prospective evaluation and review of the literature. Pharmacotherapy 16: 663–674
88. Daleau P, Lessard E, Groleau MF, Turgeon J (1995) Erythromycin blocks the rapid component of the delayed rectifier potassium current and lengthens repolarization of guinea pig ventricular myocytes. Circulation 91: 3010–3016
89. Rampe D, Murawsky MK (1997) Blockade of the human cardiac K+ channel Kv1.5 by the antibiotic erythromycin. Naunyn Schmiedeberg's Arch Pharmacol 355: 743–750
90. Stramba Badiale M, Nador F, Porta N, Guffanti S, Frediani M, Colnaghi C, Grancini F, Motta G, Carnelli V, Schwartz PJ (1997) QT interval prolongation and risk of life-threatening arrhythmias during toxoplasmosis prophylaxis with spiramycin in neonates. Am Heart J 133: 108–111
91. Stramba Badiale M, Guffanti S, Porta N, Frediani M, Beria G, Colnaghi C (1993) QT interval prolongation and cardiac arrest during antibiotic therapy with spiramycin in a newborn infant. Am Heart J 126: 740–742
92. von Rosensteil NA, Adam D (1995) Macrolide antibacterials. Drug interactions of clinical significance. Drug Saf 13: 105–122
93. van Haarst AD, van 't Klooster GA, van Gerven JM, Schoemaker RC, van Oene JC, Burggraaf J, Coene MC, Cohen AF (1998) The influence of cisapride and clarithromycin on QT intervals in healthy volunteers. Clin Pharmacol Ther 64: 542–546
94. Lee KL, Jim MH, Tang SC, Tai YT (1998) QT prolongation and Torsades de Pointes associated with clarithromycin. Am J Med 104: 395–396
95. von Seidlein L, Jaffar S, Greenwood B (1997) Prolongation of the QTc interval in African children treated for falciparum malaria. Am J Trop Med Hyg 56: 494–497
96. Monlun E, Pillet O, Cochard JF, Favarel GJ, le-Bras M (1993) Prolonged QT interval with halofantrine. Lancet 341: 1541–1542
97. Nosten F, ter Kuile FO, Luxemburger C, Woodrow C, Kyle DE, Chongsuphajaisiddhi T, White NJ (1993) Cardiac effects of antimalarial treatment with halofantrine. Lancet 341: 1054–1056
98. Sheldon R, Duff H, Koshman ML (1995) Antiarrhythmic activity of quinine in humans. Circulation 92: 2944–2950
99. Claessen FA, van-Boxtel CJ, Perenboom RM, Tange RA, Wetsteijn JC, Kager PA (1998) Quinine pharmacokinetics: ototoxic and cardiotoxic effects in healthy Caucasian subjects and in patients with falciparum malaria. Trop Med Int Health 3: 482–489
100. White NJ, Looareesuwan S, Warrell DA (1983) Quinine and quinidine: a comparison of EKG effects during the treatment of malaria. J Cardiovasc Pharmacol 5: 173–175
101. Karbwang J, Thanavibul A, Molunto P, Na BK (1993) The pharmacokinetics of quinine in patients with hepatitis. Br J Clin Pharmacol 35: 444–446
102. Po SS, Wang DW, Yang IC, Johnson JPJ, Nie L, Bennett PB (1999) Modulation of HERG potassium channels by extracellular magnesium and quinidine. J Cardiovasc Pharmacol 33: 181–185
103. Karbwang J, Davis TM, Looareesuwan S, Molunto P, Bunnag D, White NJ (1993) A comparison of the pharmacokinetic and pharmacodynamic properties of quinine and quinidine in healthy Thai males. Br J Clin Pharmacol 35: 265–271
104. Ribeiro IR, Olliaro P (1998) Safety of artemisinin and its derivatives. A review of published and unpublished clinical trials. Med Trop (Mars) 58: 50–53
105. van Agtmael MA, Gupta V, van der Wosten TH, Rutten JP, van Boxtel CJ (1999) Grapefruit juice increases the bioavailability of artemether. Eur J Clin Pharmacol 55: 405–410
106. Tinh Hien T, Day NP, Nguyen HP, Nguyen TH, Pham PL, Dinh XS, Ly VC, Ha V, Waller D, Peto TE, White NJ (1996) A controlled trial of artemether or quinine in Vietnamese adults with severe falciparum malaria. N Engl J Med 335: 76–83
107. Lode H, Vogel F, Elies W (1999) Grepafloxacin: a review of its safety profile based on clinical trials and postmarketing surveillance. Clin Ther 21: 61–74
108. Samaha FF (1999) QTc interval prolongation and polymorphic ventricular tachycardia in association with levofloxacin. Am J Med 107: 528–529
109. Anonymous (1999) Transcript of the 67th meeting of the Anti-infective Drugs Advisory Committee (October 21, 1999). FDA internet site
110. Demolis JL, Charransol A, Funck-Brentano C, Jaillon P (1996) Effects of a single oral dose of sparfloxacin on ventricular repolarization in healthy volunteers. Br J Clin Pharmacol 41: 499–503
111. Lipsky BA, Dorr MB, Magner DJ, Talbot GH (1999) Safety profile of sparfloxacin, a new fluoroquinolone antibiotic. Clin Ther 21: 148–159
112. Morganroth J, Hunt T, Dorr MB, Magner D, Talbot GH (1999) The cardiac pharmacodynamics of therapeutic doses of sparfloxacin. Clin Ther 21: 1171–1181
113. Adamantidis MM, Dumotier BM, Caron JF, Bordet R (1998) Sparfloxacin but not levofloxacin or ofloxacin prolongs cardiac repolarization in rabbit Purkinje fibers. Fundam Clin Pharmacol 12: 70–76
114. Hill SL, Evangelista JK, Pizzi AM, Mobassaleh M, Fulton DR, Berul CI (1998) Proarrhythmia associated with cisapride in children. Pediatrics 101: 1053–1056
115. Benatar A, Feenstra A, Decraene T, Vandenplas Y (1999) Cisapride and proarrhythmia in childhood. Pediatrics 103: 856–857
116. Khongphatthanayothin A, Lane J, Thomas D, Yen L, Chang D, Bubolz B (1998) Effects of cisapride on QT interval in children. J Pediatr 133: 51–56
117. Bernardini S, Semama DS, Huet F, Sgro C, Gouyon JB (1997) Effects of cisapride on QTc interval in neonates. Arch Dis Child Fetal Neonatal Ed 77: F241–F243
118. Lupoglazoff JM, Bedu A, Faure C, Denjoy I, Casasoprana A, Cezard JP, Aujard Y (1997) Allongement de l'espace QT sous cisapride chez le nouveau-né et le nourrisson. Arch Pediatr 4: 509–514
119. Rampe D, Roy ML, Dennis A, Brown AM (1997) A mechanism for the proarrhythmic effects of cisapride (Propulsid): high affinity blockade of the human cardiac potassium channel HERG. FEBS Lett 417: 28–32
120. Mohammad S, Zhou Z, Gong Q, January CT (1997) Blockage of the HERG human cardiac K+ channel by the gastrointestinal prokinetic agent cisapride. Am J Physiol 273: H2534–H2538
121. Drolet B, Khalifa M, Daleau P, Hamelin BA, Turgeon J (1998) Block of the rapid component of the delayed rectifier potassium current by the prokinetic agent cisapride underlies

drug-related lengthening of the QT interval. Circulation 97: 204–210

122. Walker BD, Singleton CB, Bursill JA, Wyse KR, Valenzuela SM, Qiu MR, Breit SN, Campbell TJ (1999) Inhibition of the human ether-a-go-go-related gene (HERG) potassium channel by cisapride: affinity for open and inactivated states. Br J Pharmacol 128: 444–450
123. Ikeda T (1994) QT prolongation in type 2 diabetes mellitus treated with glibenclamide. Diabetes Metab 20: 565–567
124. Shaffer P, Pelzmann B, Bernhart E, Lang P, Mächler H, Rigler B, Koidl B (1999) The sulphonylurea glibenclamide inhibits voltage dependent potassium currents in human atrial and ventricular myocytes. Br J Pharmacol 128: 1175–1180
125. Rosati B, Rocchetti M, Zaza A, Wanke E (1998) Sulfonylureas blockade of neural and cardiac HERG channels. FEBS Lett 440: 125–130
126. Arfiero S, Ometto R, Vincenzi M (1999) Ketanserin induced QT prolongation and torsade de pointes. Giornale Italiano di Cardiologia 20: 869–872
127. Zehender M, Meinertz T, Hohnloser S, Geibel A, Hartung J, Seiler KU, Just H (1989) Incidence and clinical relevance of QT prolongation caused by the new selective serotonin antagonist ketanserin. Am J Cardiol 63: 826–832
128. Aldariz AE, Romero H, Baroni M, Baglivo H, Esper RJ (1986) QT prolongation and torsade de pointes ventricular tachycardia produced by ketanserin. Pacing Clin Electrophysiol 9: 836–841
129. Zhang ZH, Boutjdir M, El-Sherif N (1994) Ketanserin inhibits depolarization-activated outward potassium current in rat ventricular myocytes. Circ Res 75: 711–721
130. Moss AJ, Chaikin P, Garcia JD, Gillen M, Roberts DJ, Morganroth J (1999) A review of the cardiac systemic side-effects of antihistamines: ebastine. Clin Exp Allergy 29[suppl 3]: 200–205
131. Paserchia LA, Hewett J, Woosley RL (1994) Effect of ketoconazole on QTc. Clin Pharmacol Ther 55: 146
132. Dumaine R, Roy ML, Brown AM (1998) Blockade of HERG and Kv1.5 by ketoconazole. J Pharmacol Exp Ther 286: 727–735
133. Gras J, Llenas J, Palacios JM, Roberts DJ (1996) The role of ketoconazole in the QTc interval prolonging effects of H1-antihistamines in a guinea-pig model of arrhythmogenicity. Br J Pharmacol 119: 187–188
134. Eisenhauer MD, Eliasson AH, Taylor AJ, Coyne PE J, Wortham DC (1994) Incidence of cardiac arrhythmias during intravenous pentamidine therapy in HIV-infected patients. Chest 105: 389–395
135. Dujovne CA, Atkins F, Wong B, DeCoursey S, Krehbiel P, Chernoff SB (1984) Electrocardiographic effects of probucol. A controlled prospective clinical trial. Eur J Clin Pharmacol 26: 735–739
136. Romics L, Littmann L, Laszlo Z, Fenyvesi T (1988) The effects of probucol on QT/QS2 relation and systolic time intervals. Int J Cardiol 19: 303–308
137. Ohya Y, Kumamoto K, Abe I, Tsubota Y, Fujishima M (1993) Factors related to QT interval prolongation during probucol treatment. Eur J Clin Pharmacol 45: 47–52
138. Tamura M, Ueki Y, Ohtsuka E, Oribe M, Seita M, Oribe K, Ito M (1994) Probucol-induced QT prolongation and syncope. Jpn Circ J 58: 374–377
139. Reinoehl J, Frankovich D, Machado C, Kawasaki R, Baga JJ, Pires LA, Steinman RT, Fromm BS, Lehmann MH (1996) Probucol-associated tachyarrhythmic events and QT prolongation: importance of gender. Am Heart J 131: 1184–1191
140. Johnson MC, So S, Marsh JW, Murphy AM (1992) QT prolongation and torsades de pointes after administration of FK506. Transplantation 53: 929–930
141. Sawabe T, Mizuno S, Gondo H, Maruyama T, Niho Y (1997) Sinus arrest during tacrolimus (FK506) and digitalis treatment in a bone marrow transplant recipient. Transplantation 64: 182–183
142. Calandra S (1998) Sinus arrest during tacrolimus treatment: was the QT interval prolonged? Transplantation 66: 402–404
143. Hodak SP, Moubarak JB, Rodriguez I, Gelfand MC, Alijani MR, Tracy CM (1998) QT prolongation and near fatal cardiac arrhythmia after intravenous tacrolimus administration: a case report. Transplantation 66: 535–537
144. duBell WH, Wright PA, Lederer WJ, Rogers TB (1997) Effect of the immunosuppressant FK506 on excitation-contraction coupling and outward K+ currents in rat ventricular myocytes. J Physiol (Lond) 501: 509–516
145. Pollack IF, DaRosso RC, Robertson PL, Jakacki RL, Mirro JRJ, Blatt J, Nicholson S, Packer RJ, Allen JC, Cisneros A, Jordan VC (1997) A phase I study of high-dose tamoxifen for the treatment of refractory malignant gliomas of childhood. Clin Cancer Res 3: 1109–1115
146. Trump DL, Smith DC, Ellis PG, Rogers MP, Schold SC, Winer EP, Panella TJ, Jordan VC, Fine RL (1992) High-dose oral tamoxifen, a potential multidrug-resistance-reversal agent: phase I trial in combination with vinblastine. J Natl Cancer Inst 84: 1811–1816
147. Liu XK, Katchman A, Ebert SN, Woosley RL (1998) The antiestrogen tamoxifen blocks the delayed rectifier potassium current, IKr, in rabbit ventricular myocytes. J Pharmacol Exp Ther 287: 877–883
148. Connolly MJ, Astridge PS, White EG, Morley CA, Cowan JC (1991) Torsades de pointes ventricular tachycardia and terodiline. Lancet 338: 344–345
149. Stewart DA, Taylor J, Ghosh S, Macphee GJ, Abdullah I, McLenachan JM, Stott DJ (1992) Terodiline causes polymorphic ventricular tachycardia due to reduced heart rate and prolongation of QT interval. Eur J Clin Pharmacol 42: 577–580
150. Hartigan-Go K, Bateman DN, Daly AK, Thomas SH (1996) Stereoselective cardiotoxic effects of terodiline. Clin Pharmacol Ther 60: 89–98
151. Jones SE, Ogura T, Shuba LM, McDonald TF (1998) Inhibition of the rapid component of the delayed-rectifier K+ current by therapeutic concentrations of the antispasmodic agent terodiline. Br J Pharmacol 125: 1138–1143
152. Shuba LM, Kasamaki Y, Jones SE, Ogura T, McCullough JR, McDonald TF (1999) Action potentials, contraction, and membrane currents in guinea pig ventricular preparations treated with the antispasmodic agent terodiline. J Pharmacol Exp Ther 290: 1417–1426
153. Jones SE, Kasamaki Y, Ogura T, Shuba LM, McCullough JR, McDonald TF (1999) Inhibition of cardiac inward-rectifier K+ current by terodiline. Eur J Pharmacol 370: 319–327
154. Pressler ML, Warner MR, Rubart M, Rardon DP, Zipes DP (1995) In vivo and in vitro electrophysiologic effects of terodiline on dog myocardium. J Cardiovasc Electrophysiol 6: 443–454
155. Pratt CM, Ruberg S, Morganroth J, McNutt B, Woodward J, Harris S, Ruskin J, Moye L (1996) Dose-response relation between terfenadine (Seldane) and the QTc interval on the scalar electrocardiogram: distinguishing a drug effect from spontaneous variability. Am Heart J 131: 472–480
156. Honig PK, Woosley RL, Zamani K, Conner DP, Cantilena LRJ (1992) Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. Clin Pharmacol Ther 52: 231–238
157. Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena-LR J (1990) Torsades de pointes occurring in association with terfenadine use. JAMA 264: 2788–2790
158. Zimmermann M, Duruz H, Guinand O, Broccard O, Levy P, Lacatis D, Bloch A (1992) Torsades de Pointes after treatment with terfenadine and ketoconazole. Eur Heart J 13: 1002–1003
159. Honig PK, Wortham DC, Zamani K, Conner DP, Mullin JC, Cantilena LR (1993) Terfenadine-ketoconazole interaction. Pharmacokinetic and electrocardiographic consequences. JAMA 269: 1513–1518

160. Honig PK, Wortham DC, Hull R, Zamani K, Smith JE, Cantilena LR (1993) Itraconazole affects single-dose terfenadine pharmacokinetics and cardiac repolarization pharmacodynamics. J Clin Pharmacol 33: 1201–1206
161. Honig PK, Wortham DC, Lazarev A, Cantilena LR (1996) Grapefruit juice alters the systemic bioavailability and cardiac repolarization of terfenadine in poor metabolizers of terfenadine. J Clin Pharmacol 36: 345–351
162. Sakemi H, VanNatta B (1993) Torsade de pointes induced by astemizole in a patient with prolongation of the QT interval. Am Heart J 125: 1436–1438
163. Hsieh MH, Chen SA, Chiang CE, Tai CT, Lee SH, Wen ZC, Chang MS (1996) Drug-induced torsades de pointes in one patient with congenital long QT syndrome. Int J Cardiol 54: 85–88
164. Tsai WC, Tsai LM, Chen JH (1997) Combined use of astemizole and ketoconazole resulting in torsade de pointes. J Formos Med Assoc 96: 144–146
165. Adamantidis MM, Lacroix DL, Caron JF, Dupuis BA (1995) Electrophysiological and arrhythmogenic effects of the histamine type 1-receptor antagonist astemizole on rabbit Purkinje fibers: clinical relevance. J Cardiovasc Pharmacol 26: 319–327
166. Woosley RL, Chen Y, Freiman JP, Gillis RA (1993) Mechanism of the cardiotoxic actions of terfenadine. JAMA 269: 1532–1536
167. Roy M, Dumaine R, Brown AM (1996) HERG, a primary human ventricular target of the nonsedating antihistamine terfenadine. Circulation 94: 817–823
168. Ducic I, Ko CM, Shuba Y, Morad M (1997) Comparative effects of loratadine and terfenadine on cardiac K+ channels. J Cardiovasc Pharmacol 30: 42–54
169. Sorkin EM, Heel RC (1985) Terfenadine. A review of its pharmacodynamic properties and therapeutic efficacy. Drugs 29: 34–56
170. Heykants J, Van Peer A, Woestenborghs R, Jageneau A, Vanden Bussche (1986) Dose-proportionality, bioavailability, and steady-state kinetics of astemizole in man. Drug Dev Res 8: 71–78
171. Honig PK, Wortham DC, Zamani K, Cantilena LR (1994) Comparison of the effect of the macrolide antibiotics erythromycin, clarithromycin and azithromycin on terfenadine steady-state pharmacokinetics and electrocardiographic parameters. Drug Invest 7: 148–156
172. Pohjola-Sintonen S, Viitasalo M, Toivonen L, Neuvonen P (1993) Itraconazole prevents terfenadine metabolism and increases risk of torsades de pointes ventricular tachycardia. Eur J Clin Pharmacol 45: 191–193
173. Crane JK, Shih HT (1993) Syncope and cardiac arrhythmia due to an interaction between itraconazole and terfenadine. Am J Med 95: 445–446
174. Benton RE, Honig PK, Zamani K, Cantilena LR, Woosley RL (1996) Grapefruit juice alters terfenadine pharmacokinetics, resulting in prolongation of repolarization on the electrocardiogram. Clin Pharmacol Ther 59: 383–388
175. Clifford CP, Adams DA, Murray S, Taylor GW, Wilkins MR, Boobis AR, Davies DS (1997) The cardiac effects of terfenadine after inhibition of its metabolism by grapefruit juice. Eur J Clin Pharmacol 52: 311–315
176. Lefebvre RA, Van Peer A, Woestenborghs R (1997) Influence of itraconazole on the pharmacokinetics and electrocardiographic effects of astemizole. Br J Clin Pharmacol 43: 319–322
177. Goodman LS, Gilman A (1996) The pharmacological basis of therapeutics, 9th edn. McGraw-Hill, New York
178. Slater JW, Zechnich AD, Haxby DG (1999) Second-generation antihistamines: a comparative review. Drugs 57: 31–47
179. Knight BP, Pelosi F, Michaud GF, Strickberger SA, Morady F (1999) Clinical consequences of electrocardiographic artifact mimicking ventricular tachycardia. N Engl J Med 341: 1270–1274
180. Murakawa Y, Yamashita T, Ajiki K, Sezaki K, Omata M (1998) Ostensible day-night difference of QT prolongation during long-term treatment with antiarrhythmic drugs: reappraisal of the law of "regression to the mean". J Cardiovasc Pharmacol 32: 62–65